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CONGENITAL ARRHYTHMIAS AND CONDUCTION ABNORMALITIES IN A FATHER AND FOUR CHILDREN*

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FIVE MEMBERS of one family, the father and four of his six children, presented abnormalities of cardiac rhythm and conduction. During a clinical experience of about 30 years only one other analogous experience has been encountered: a family in which three generations, mother, daughter and grandson (aged 6), had paroxysmal atrial tachycardia in the absence of any signs of valvular or myocardial disease. Increasing numbers of similar cases have been reported in recent years;[1] they may be less rare than our experience suggests.

The father, Mr. Joseph W., had white and Negro ancestors who settled in the Gaspé region of Quebec, where he was born in 1884. He could recall no illnesses of childhood. He had an appendectomy in 1939, surgical treatment for an abscess in the right side of the neck in 1932, and left-sided pneumonia in 1934. He married at the age of 22. His wife and six children are alive and "well"; eleven children died in infancy. His father died at the age of 90 and his mother at the age of 80 years. In 1959 one sister 82 years of age and one brother 71 were alive and quite well. One brother had died at the age of two years, of undetermined cause; one sister died at 26 of tuberculosis; one brother died of accidental injuries; one brother died at 48, of undetermined cause; and four siblings died in youth, also of undetermined causes.

This patient came to our attention on January 11, 1946, referred by the Canadian National Railway Clinic, because of fainting spells which began in July 1945. The first of these occurred while he was at work. It was very brief. He described it as a sense of impending faintness. He sat down, recovered and resumed his activities. Subsequently, he recognized warning symptoms, a sense of a lump under the sternum which rose to the neck as a burning sensation, then an ache in the occipital region, followed by loss of consciousness for a few moments. This recurred daily. The maximum number of such episodes was nine in one day. He stopped working on August 4, 1945.

Physical examination on January 11, 1946, revealed a healthy looking man 62 years of age, 6 feet 3 inches tall, weighing 170 lb. The liver edge was felt 3 cm. below the costal border but there was no evidence of congestive cardiac failure. The transverse diameter of the heart by orthodiagram was 17 cm. and that of the chest was 30 cm. This marked cardiac enlargement was judged to be symmetrical and was associated with hypertension, the arterial pressure being 170 mm. Hg systolic and 120 diastolic. There was no evidence of luetic cardiovascular disease. The electrocardiogram revealed atrial flutter with varying degrees of block, mainly 2:1, with a ventricular rate of 57 to 85 per minute and right bundle branch block. Occasional ventricular ectopic beats occurred. He was digitalized and four months later reported that he had not had any fainting spells and wished to return to work. At that time the electrocardiogram revealed sinus rhythm interrupted by either sinus block and ventricular escape or nodal rhythm with P waves masked by QRS complexes. These peculiarities led to discontinuing digitalis. A month later, the electrocardiogram revealed atrial flutter with an auricular rate of 186 and a ventricular rate of 93 per min. Carotid sinus pressure slowed the ventricular rate to the equivalent of 20 per minute for a few seconds. In August 1946, after having had no medicinal therapy since April, he reported brief recurrences of faintness, but no loss of consciousness. These occurred rarely and were usually related to performing heavy chores in the house. The electrocardiogram (Fig. 1) showed an atrial rate of 180 with a ventricular rate of 90, but the atrial waves resembled those of paroxysmal tachycardia and not of flutter. Carotid sinus pressure did not reduce the heart rate or alter the atrial rhythm. Quinidine sulfate therapy was considered but was not given. It was recommended that he should return to a light, non-hazardous job.

In May 1947, he reported that he had worked all winter as a stationary engineer and had been free from any fainting spells. On this occasion the atrial complexes were again those of flutter, but

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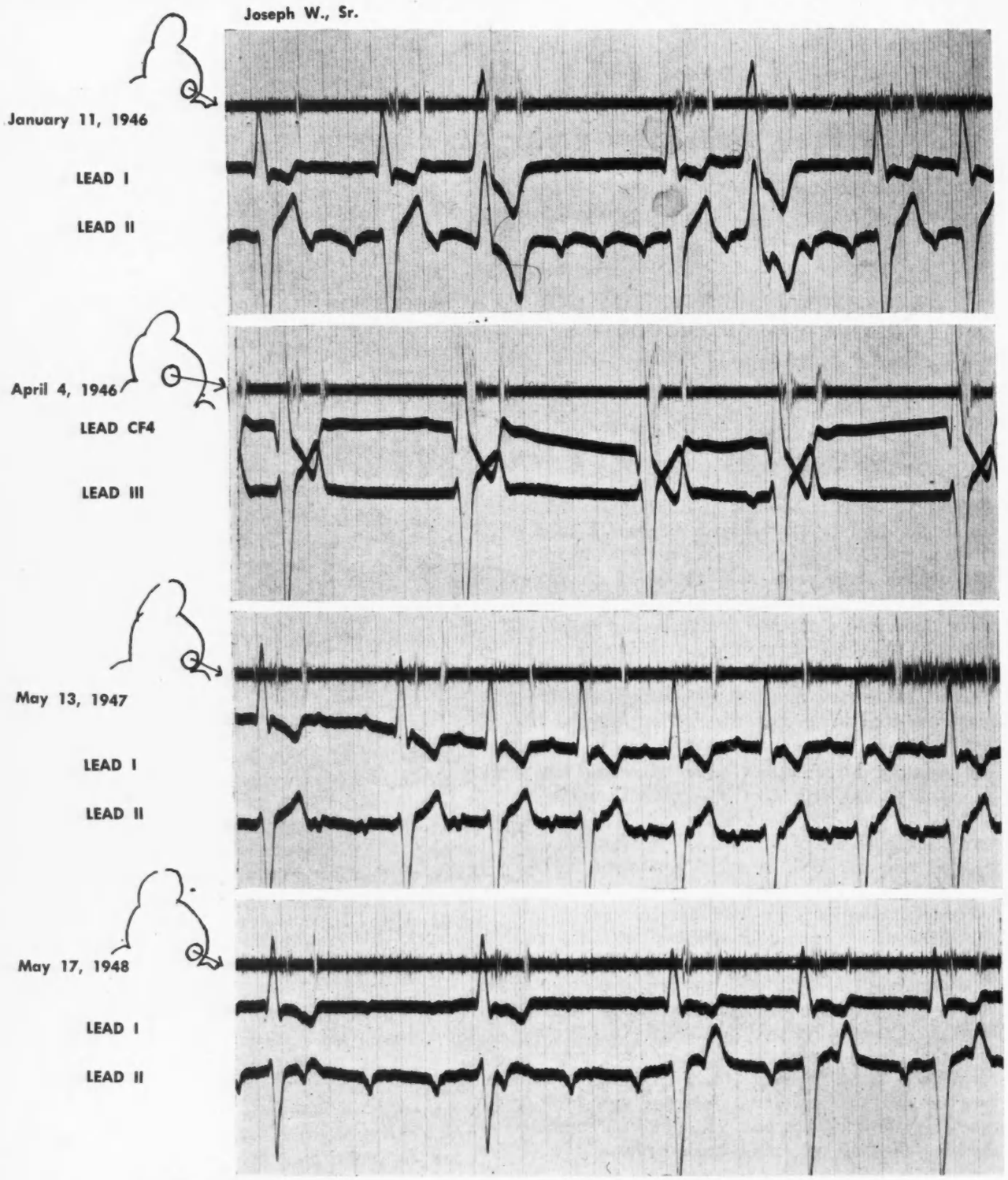

Fig. 1.—(Joseph W., Sr.) The QRS complexes remain constant in shape but the atrial rhythm changes. On January 11, 1946, the atrial waves strongly resemble flutter waves but the rate is only 187 per minute. Flutter waves are found in the record of May 1948, with a rate of 166. On May 13, 1947, the atrial waves are compatible with flutter or paroxysmal atrial tachycardia from an ectopic focus. On all three occasions there was partial A-V block, varying between 2:1 and 3:1. On January 11, 1946, there were also ventricular ectopic beats. On April 4, 1946, the rhythm is either nodal or there is atrial standstill with ventricular escape for several beats, then atrial contractions are resumed. The pattern presented here repeated itself several times in the record, so that an atrial beat made its appearance about every three seconds.

There is some variation in loudness of the first heart sound in all these records. This is associated with differences in time between atrial and ventricular contraction. The first sound on January 11, 1946, was mainly of low amplitude, in some instances so low that it was almost inaudible. F-R interval is mainly about 0.20 sec. but was somewhat longer for the very first beat in this strip. On April 4, 1946, the first sound has a higher amplitude with those beats for which there is no obvious P-wave than for the one beat with a P-R interval of 0.20 sec. This suggests that the beats with the louder first sound may be nodal beats, the atrial contraction occurring at about the same time as the ventricular contraction. On May 13, 1947, and May 17, 1948, the first sound is again of low amplitude for all beats recorded and the F-R interval is about 0.24-0.30 sec.

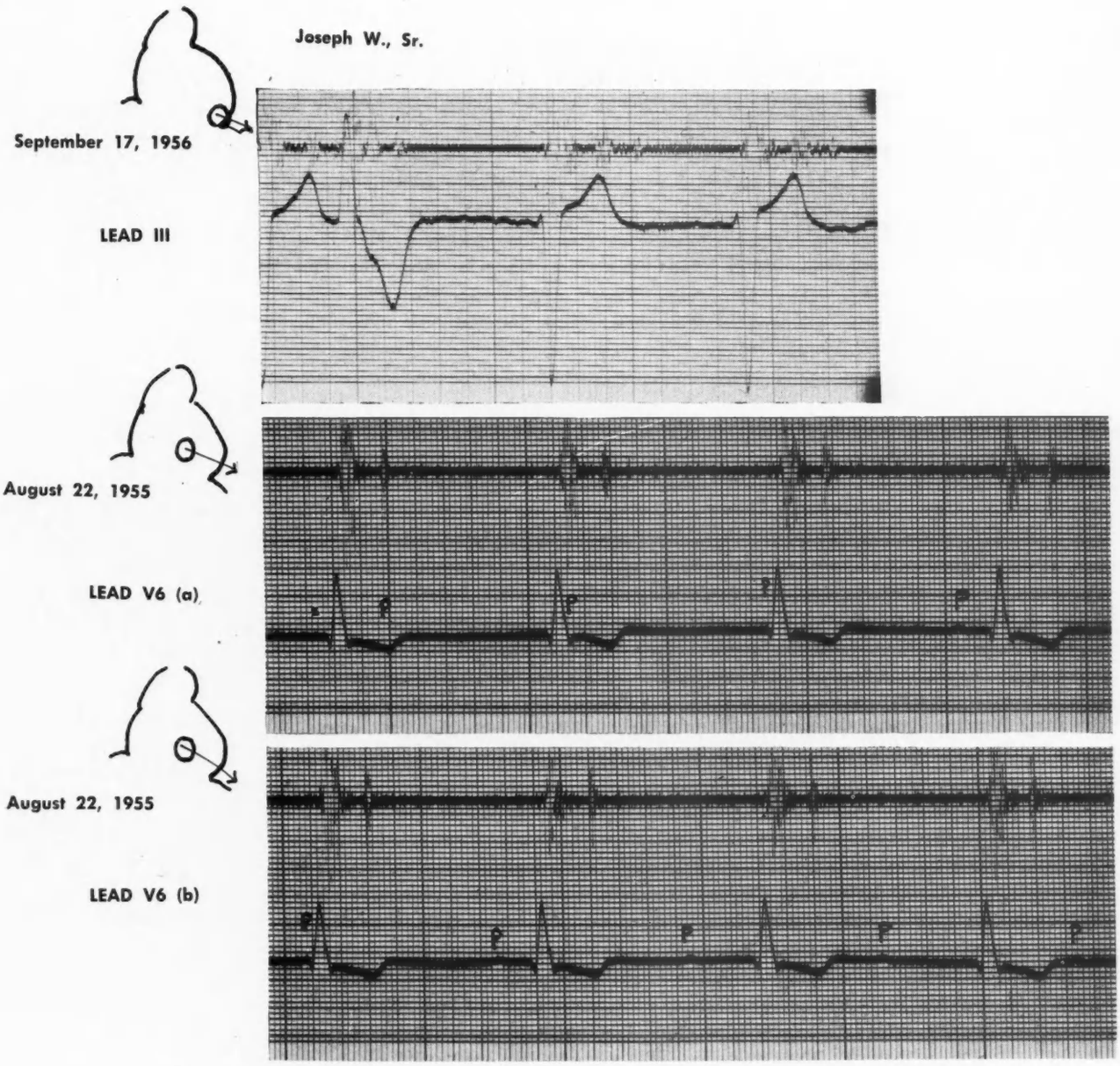

Fig. 2.—(Joseph W., Sr.) On August 22, 1955, sinus bradycardia with complete A-V dissociation is seen in records (a) and (b) which are consecutive. On September 17, 1956, there is complete A-V dissociation, with atrial fibrillation and occasional ventricular ectopic beats. On August 22, 1955, the amplitude of the first heart sound varies less with variations in the duration of the P-R interval than in previous records and less than might be expected. No clear explanation for this can be offered.

the rate was only 150 per minute with 2:1 block and a constant ventricular rate of 75. Carotid sinus pressure readily slowed the ventricular rate and revealed the atrial waves. The blood pressure of 200 mm. Hg systolic and 140 diastolic was higher than at any other time. No medication was prescribed. In February 1949, he reported that he had been working regularly and had felt better than ever. He could walk three miles to and from work with no discomfort. He was 65 years old and he was due to retire in the near future. The blood pressure at that time was 200 systolic and 70 diastolic. The electrocardiogram revealed nodal rhythm with occasional ventricular escape; no change in shape of the ventricular complexes could be found. In 1956 he reported that he was enjoying good health in retirement and that his only disability was impaired vision. This was controlled by the prescription of corrective lenses. In June 1957, a suprapubic cystostomy was performed for obstructive symptoms, and in August 1957, a transurethral resection of the prostate was carried out. In May 1959, he had an episode of loss of consciousness which lasted for two hours and he recovered completely. Two weeks later, he had a period of unconsciousness which persisted for an hour and again he recovered spontaneously. On this occasion he was brought to the hospital and was found to have disturbances in speech and in the function of the right upper and lower extremities, which indicated that there had been significant brain damage due to cerebral ischemia resulting in some impairment in function but without well-defined localizing signs of an upper motor neuron syn-

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Fig. 3.—(Joseph W., Sr.) The pattern of QRS and T-waves in this record is the same as in all records made since January 11, 1946. There is right bundle branch block with evidence of left ventricular enlargement. There is atrial fibrillation, and this makes for little or no variation in the loudness of the first sound from beat to beat. Note third sound at apex and split second sound at left border of sternum at fourth space in the cycle of V5.

drome. In July 1959, while convalescing at home, he died suddenly. No autopsy was performed.

On August 8, 1955, the name of Joseph W. appeared on my appointment list and with great interest I looked forward to studying this man after an interval of more than six years. But the patient proved to be a young man of 34, his son. One may imagine with what clinical curiosity I listened to this young man's story which I recorded in notes that are best quoted verbatim. "When he is working, and he is a wood machinist at the Canadian Pacific Railway Shops, he feels perfectly well.

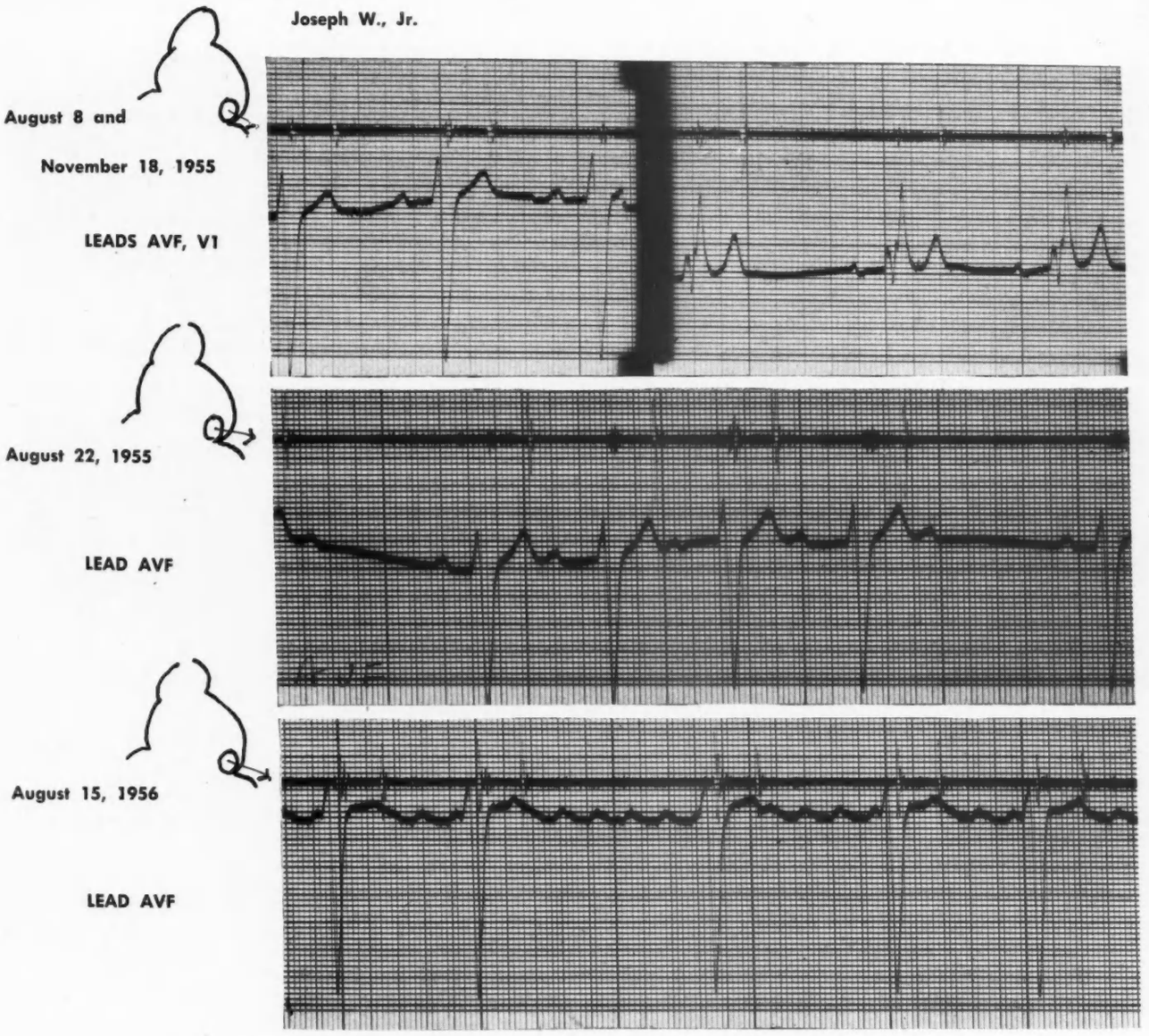

Fig. 4.—(Joseph W., Jr.) The record of November 18, 1955, is similar to that of August 8, 1955. There is the pattern of right bundle branch block and partial A-V block with a P-R interval of 0.28 sec. On August 22, 1955, there was partial A-V block with occasional dropped beats. This strip of record reveals a Wenckebach period, which recurred several times in the total record. As the P-R interval at its shortest is 0.28 sec., the first heart sound is relatively faint with all beats. The atrial sounds were not recordable. On August 15, 1956, there is atrial flutter, more typically than in the father's record. Atrial rate is 250 per minute; partial A-V block of varying degree, from 3:1 to 5:1. There is some variation in the loudness of the first sound, determined by the duration of the F-R interval. With short intervals the first sound is louder; with somewhat longer intervals it is less loud.

When he is among people, as for example, a few days ago when visiting a large groceteria with his friends, he had an attack in which his blood rushes to the head, he feels that his limbs are made of rubber, he sweats, and if he persists in walking or standing he falls to the ground in a faint, with loss of consciousness but only for a few seconds. When he awakens he feels perfectly well again. He has had about a dozen of these attacks since the first one which occurred a year ago. This attack occurred while he was in the woods hunting. He has had three while walking on the street. He had one at a wedding. He has not had any full-blown attacks in church, but yesterday, Sunday, he had to go out of church because he felt it was too stuffy and hot. He thought he might have an attack if he stayed in. He has had no sensations of palpitation, shortness of breath or pain associated with these attacks or on other occasions. He is as unaware of his heart beat immediately after one of these attacks as before it. During these episodes he has not felt his heart with his hand because he has not noticed anything unusual about it."

This young man was born in New Carlisle. He had had measles as a child and an appendectomy in 1924 but no other illness. He married at the age of 23; his wife and four children are alive and well. Physical examination revealed a sturdy man of 34 with little trace of his paternal African ancestry. His weight was 176 lb. and his height 5′ 11½″. All physical signs were normal except those of the cardiovascular system. The heart size was within the range of normal (aortic arch 5.8 cm., right

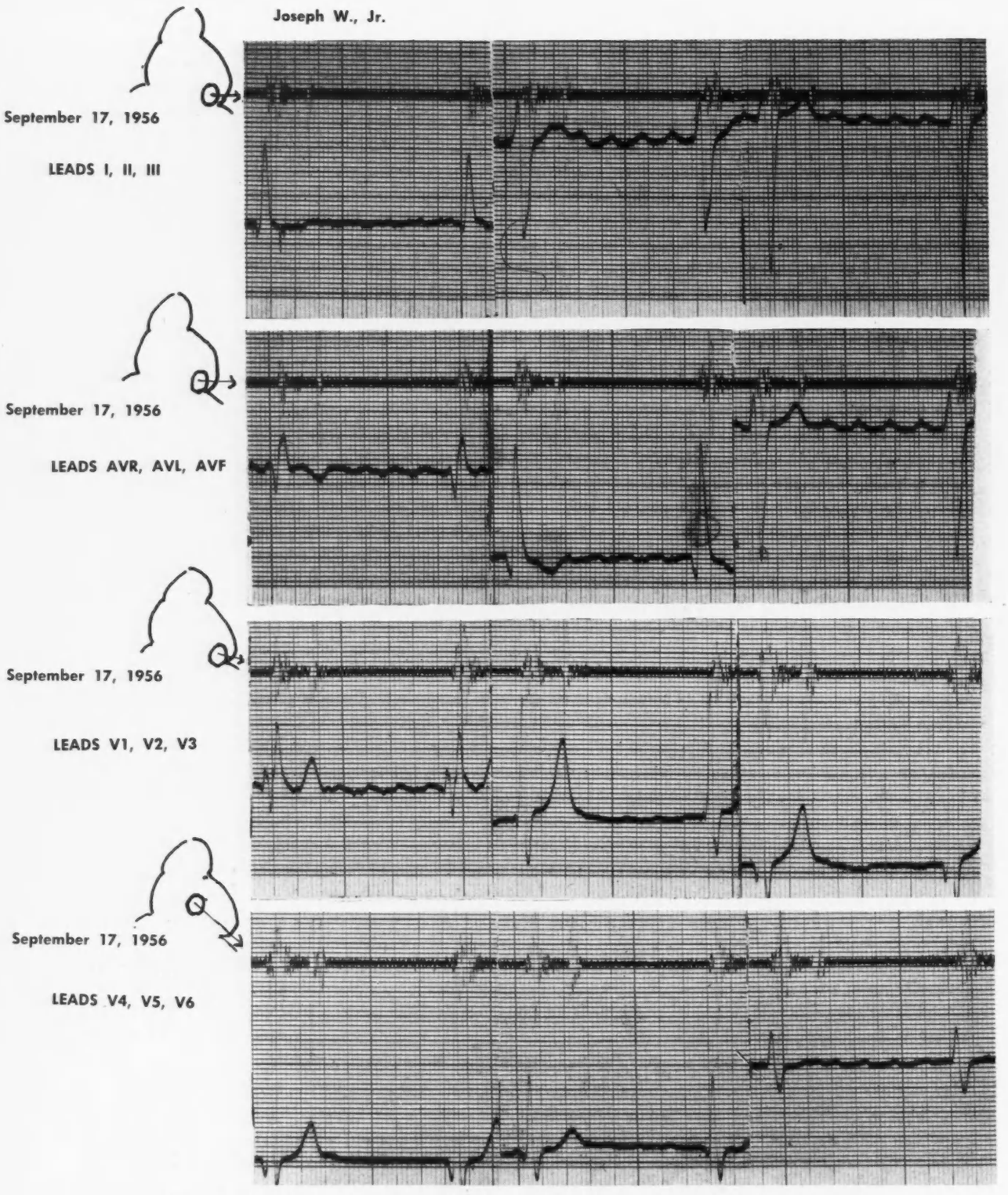

Fig. 5.—(Joseph W., Jr.) The pattern of QRS and T-complexes in 12 leads is similar to what was recorded in all records since August 8, 1955. It is very similar to the pattern recorded in the father (see Fig. 3). The differences are due to the fact that the father has a cor bovinum and the son has a heart of about normal size. Phonocardiogram reveals some variations in the loudness of the first sound, associated with differences in F-R relations.

border 5.7 cm., left border 7.8 cm., transverse diameter of the chest 30 cm.). No thrills or abnormal pulsation could be detected. The heart sounds are best described as illustrated in Fig. 11. The principal feature is relative faintness of the first sound suggestive of a long P-R interval, and splitting of the second sound with the second component a faint short, sharp sound. This type of splitting suggested right bundle branch block. The electrocardiogram (Fig. 4) revealed sinus rhythm with a P-R interval of 0.24 sec. and right bundle branch block with a pattern of ventricular complexes similar to that found in his father's electrocardiogram.

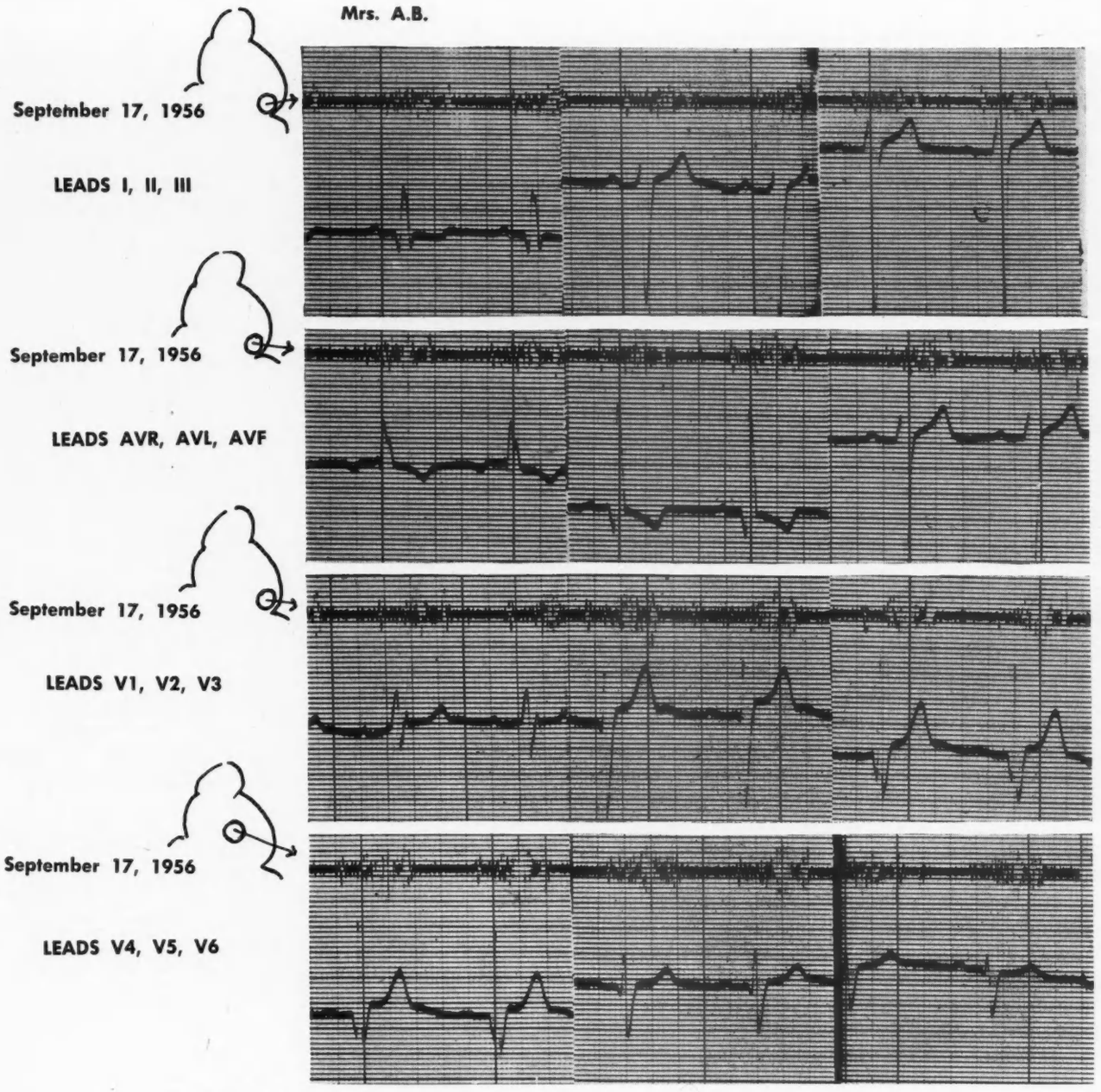

Fig. 6.—(Mrs. Alberta B.) Normal rhythm. Rate 60 per min. Partial A-V block, P-R interval 0.24 to 0.26 sec. Right bundle branch block similar to that of Joseph W., Jr.

Whereas in his father's case it was assumed that the abnormalities were due to hypertensive and arteriosclerotic heart disease, the etiology in the case of the son seemed most likely congenital and casts doubts on the diagnosis in the father's case. On the assumption that the episodes of fainting were due to transient higher degrees of A-V block, ephedrine hydrochloride ¼ grain every six hours for two weeks was prescribed. Arrangements were made to examine other members of the family.

During the year 1955-1956, Joseph Jr. had occasional but frightening recurrences of brief periods of loss of consciousness in spite of ephedrine hydrochloride and isoproterenol HCl (Isuprel) therapy. He was treated by several physicians. One of these who witnessed an episode of faintness, during which he found the pulse to be strong and regular, assured him that he was suffering from nervousness and prescribed a mild sedative. This occurred on July 10, 1956.

My examination on August 15, 1956, revealed atrial flutter with varying degrees of block and a ventricular rate of 45 to 60 (Fig. 5). To complete the resemblance to his father, he had yet to show nodal rhythm, atrial fibrillation with complete A-V dissociation and also to live to the age of 76. He made a good start by returning to work at a somewhat lighter job than his usual one at the Canadian Pacific Railway Shops.

In the last months of 1956 he was observed at the Maisonneuve Hospital, Montreal, having been admitted because of recurrent fainting spells. A few months later, in 1957, he was treated at the Royal Victoria Hospital, Montreal, and in March

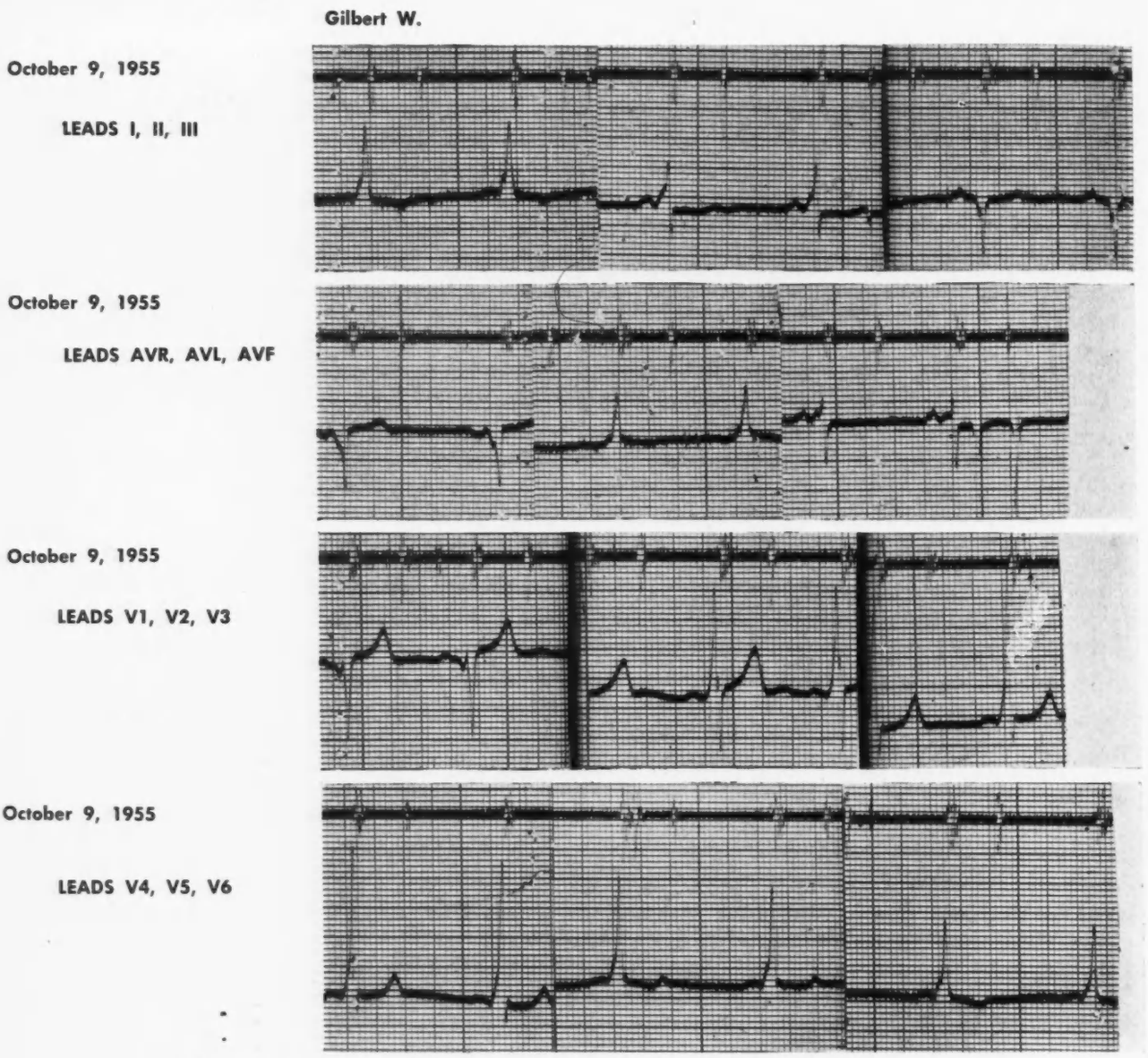

Fig. 7.—(Gilbert W.) Normal rhythm. Rate 60 per min. P-R interval 0.10 to 0.12 sec. QRS 0.10 to 0.12 sec. Wolff-Parkinson-White syndrome.

of 1958, he was readmitted to that hospital. He had not worked since 1956 because he feared imminent loss of consciousness. The anxiety state became dominant and more disabling than the Adams-Stokes syndrome which occurred once in several weeks or months and from which he recovered spontaneously. Accordingly, he was referred for psychotherapy at the Allan Memorial Institute in June 1958. No significant change in his mental condition occurred, and as Adams-Stokes attacks reappeared he was again admitted to the Royal Victoria Hospital in July 1958. One day after he was discharged from this hospital in August 1958, he entered the Montreal General Hospital for the first time and remained there for almost a year. He was studied and treated by cardiologists, internists and psychiatrists. He had numerous attacks of Adams-Stokes syndrome during certain periods of time, varying from a few days to about two weeks. As many as 30 attacks a day at the maximum would occur. The dominant atrial rhythm was auricular flutter. On other occasions, atrial paroxysmal tachycardia was found with partial or complete A-V block. Occasionally, sinus rhythm with partial A-V block was found. An external pacemaker was used on a number of occasions but usually the attacks were of the type from which he might recover spontaneously. On rare occasions when the attacks lasted for as long as one-half hour, the pacemaker was effective in saving his life. By June 1959, his mental state became very troublesome. He resented the people in the hospital and became violently antagonistic to them. He was discharged from the hospital and took along with him an early model of the external pacemaker which was to be used by his family when necessary. However, he returned to the hospital in July 1959, and during this admission, which lasted about a month, a small external pacemaker with cardiac electrodes applied to the myo-

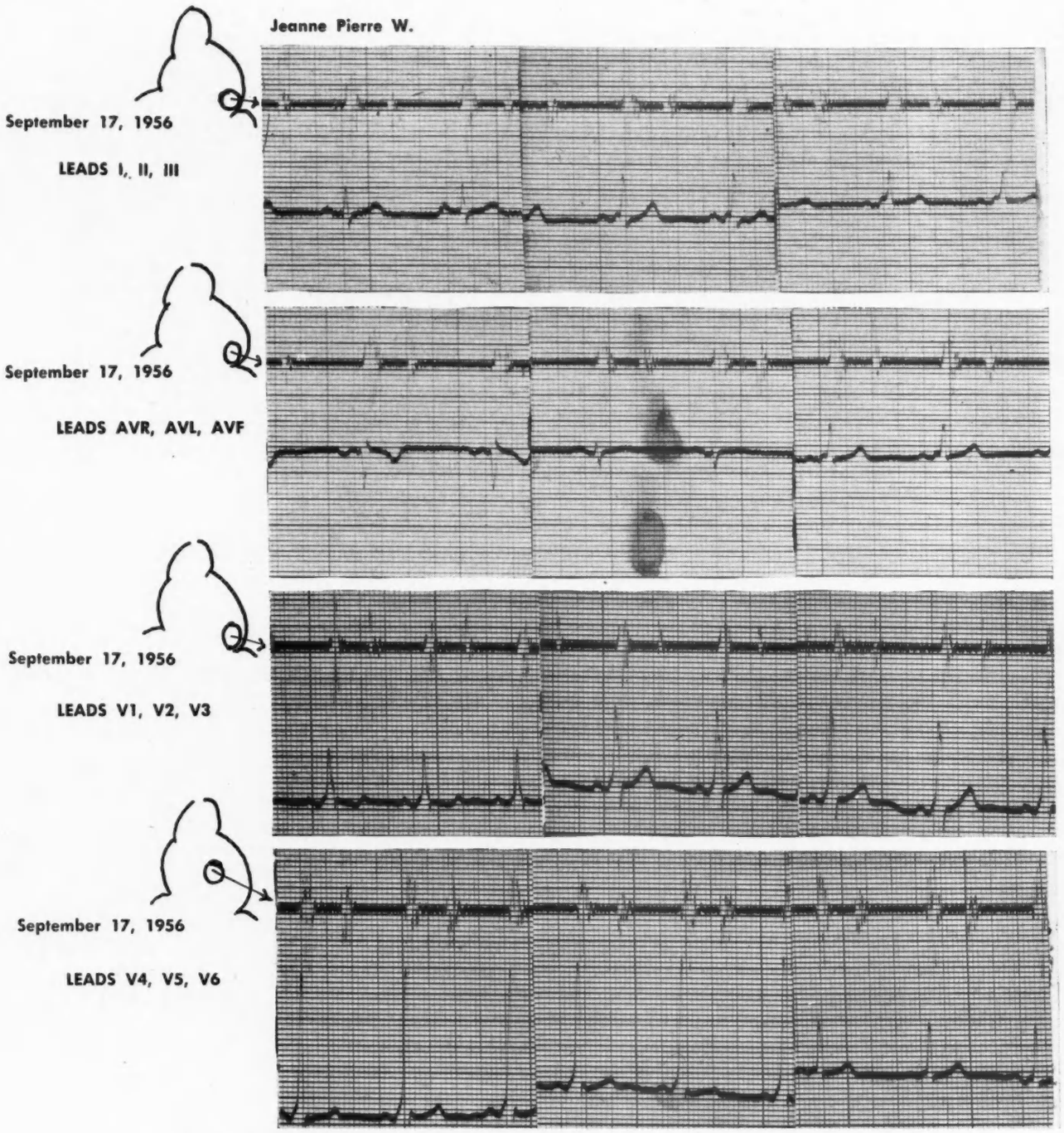

Fig. 8.—(Jean-Pierre W.) Normal rhythm. Rate 62-78 per min. P-R interval 0.12 sec. QRS 0.10 to 0.12 sec. A slurred upstroke of R in all leads except lead 1. Wolff-Parkinson-White syndrome, less grossly obvious than in Fig. 7.

cardium was "installed". Some technical difficulties made it necessary to remove this device. He had pain from a hematoma in the pericardium and pleura. At this time he was having about 10 minor attacks a month. He spent most of his time at home in bed; he feared standing up. Subsequently, he was re-admitted, cardiac electrodes were inserted again (this time more effectively), and he has been wearing this small pacemaker for about a year. The attacks have decreased greatly in frequency; spells of faintness have recurred but they have been brief. He remains totally disabled because of his emotional state, which is dominated by anxiety. During the course of the clinical investigations, a search was made for evidence of thyrotoxicosis, but none could be established. In October 1960, the electrocardiogram revealed sinus rhythm at a rate of 80 per minute, with his usual pattern of right bundle branch block.

Alberta (Mrs. Aurélien B., Joseph Sr.'s daughter), was born in 1911. She gave a history of an abscess in the right groin at 10 years of age, measles at 14, and pneumonia at 16. She had an arterial pressure of 200 mm. Hg at 20 years of age but her history contained no mention of hypertension since. She consulted her family doctor for dyspepsia at the age of 21, at which time her physician men-

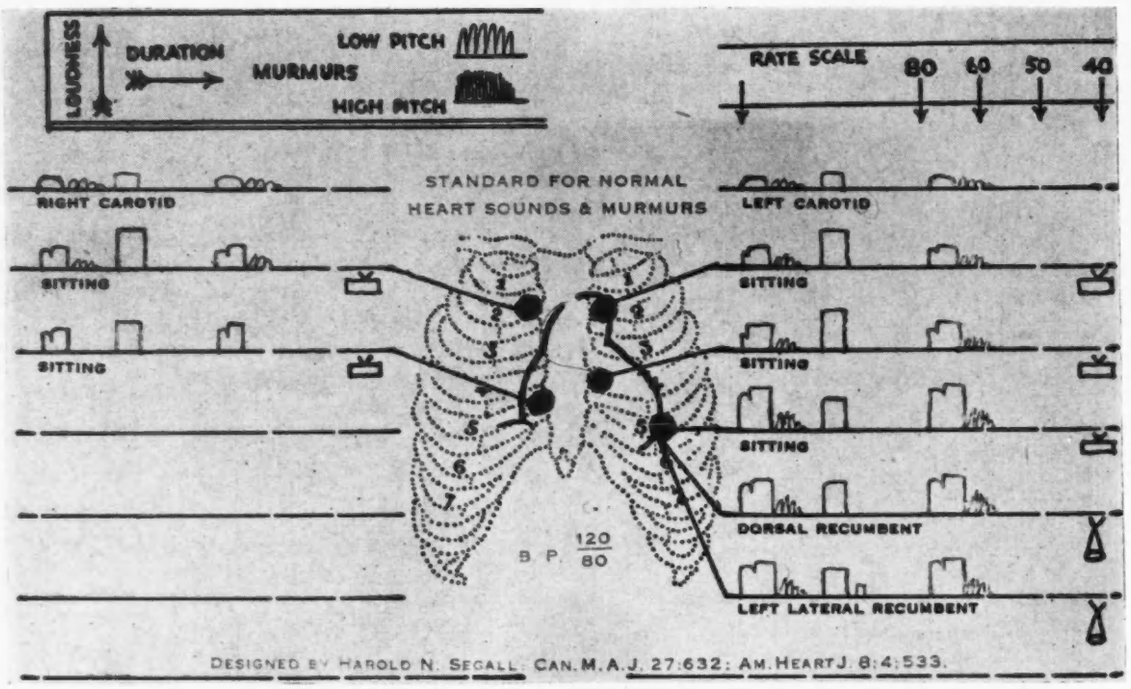

Fig. 9.—Heart Sound Chart for writing quantitative symbols for sounds and murmurs. The heart sounds and murmurs are described by the method of writing quantitative symbols while listening.[9-11] The ordinate of the rectangle represents loudness and the abscissa duration. Low-pitched, coarse murmurs are described with more widely spaced waves of vertical lines and high-pitched blowing murmurs with closely packed vertical lines. These rules are depicted in the left-hand upper segment. An arbitrary scale in the right-hand upper segment guides in representing heart rate by depicting the duration of diastole in the cardiac cycle. The faintly printed symbols represent the modal pattern of normal which was derived from a study of 100 selected normals. These guide in writing the symbols for sounds heard in the person being examined to describe quantitatively relative loudness and duration of the sounds and murmurs.

tioned that she had a heart murmur. Quinzy at 31 was treated surgically. She had a nervous breakdown at the age of 32 years. A fainting spell had occurred at age 20 and another at age 29; no details of these were recalled. She married at 29 and had no pregnancies; she kept house for her husband and his two siblings, a brother and a sister who are deaf-mutes, and an adopted son aged 7 in 1955. When she was examined on October 9, 1955, she considered that she was in good health except for dyspepsia; this had been investigated and no gastric or duodenal ulcer was demonstrated. She had no symptoms or signs of impairment in cardiac function. On physical examination she was a brunette type of well-developed woman who presented no obvious signs of Negro ancestry. The heart size and shape were normal by orthodiagram (aortic arch 4.8 cm., transverse diameter of heart 12.5 cm. and of chest 26 cm.). No abnormal pulsations could be detected but a faint systolic thrill was felt at the left border of the sternum near the fourth intercostal space and at the aortic area. The heart sounds and murmurs are best described by quantitative symbols as illustrated in Fig. 12. The arterial pressure was 126/60 mm. Hg. These signs could be attributed either to aortic stenosis or to a small interventricular septal defect. The electrocardiogram (Fig. 6) resembles those of the two Josephs, constituting a third case of right bundle branch block of peculiar type in the one family.

In June 1956, she entered the Hôtel-Dieu Hospital, Montreal, because of gastrointestinal symptoms, epigastric pain and postprandial vomiting. On the fifth day after admission, she suddenly felt a sense of impending loss of consciousness. This lasted a few seconds and was followed by severe headache and twitching of the arms and legs for some minutes, recurring several times after brief intervals of quiescence. The resident physician suspected that she was suffering from hypoglycemia. One fasting blood sugar estimation was 97 mg. %. In May 1959, while walking on the street, she suddenly, without warning aura, lost consciousness and was brought to the Hôtel-Dieu Hospital. There, recurrences revealed that she was suffering from Adams-Stokes syndrome. In September 1960, she was admitted to the Montreal General Hospital for recurrence of these attacks of loss of consciousness, 15 of which had occurred since May 1959. The electrocardiogram revealed sinus rhythm at a rate of 100 per minute, complete A-V dissociation, a ventricular rate of 20 per minute, and ventricular complexes similar to those of October 1955. Because of her anxious state and somewhat prominent eyes, a search was made for evidence of thyrotoxicosis but none was found. As in the cases of her father and brother Joseph, the exclusion test for lues was negative. The cardiac silhouette in two radiographic studies revealed no abnormalities. During the 39 days of her stay in hospital, she had a few brief "dizzy spells" but only one short attack of unconsciousness which

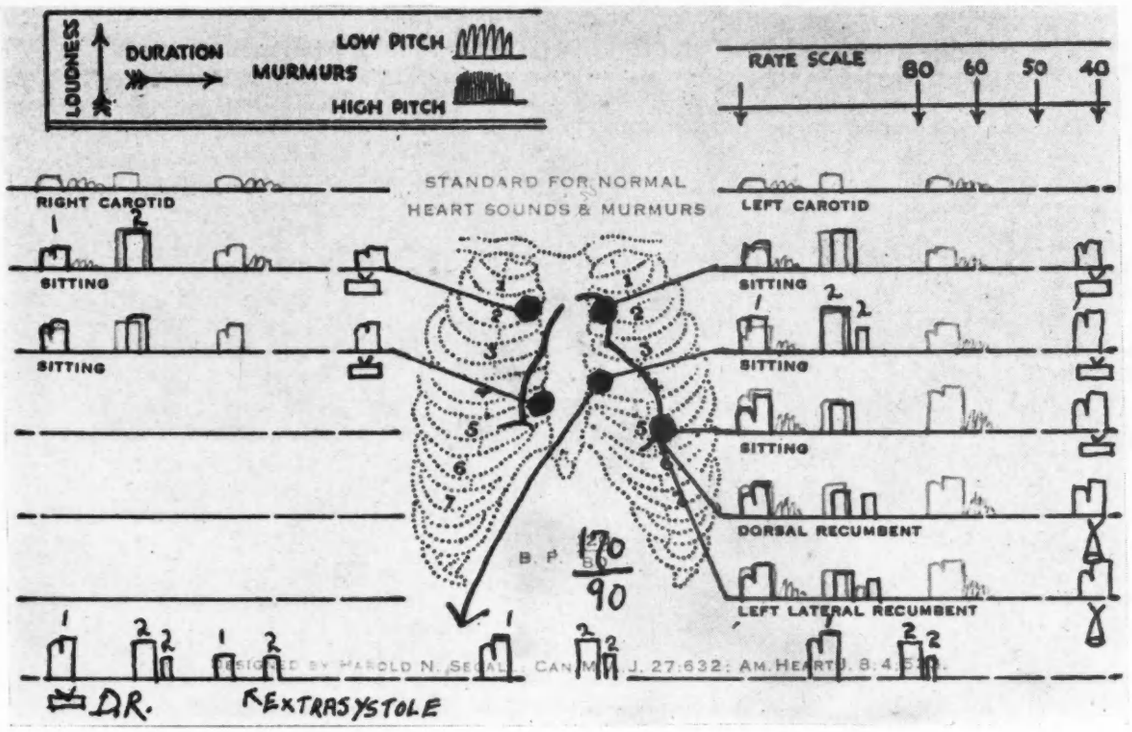

Fig. 10.—(Joseph W., Sr.) The electrocardiogram recorded on the occasion of this observation appears in Fig. 3. Splitting of the first sound is of the type found with normal intraventricular conduction but splitting of the second sound at the left border of the sternum near the fourth intercostal space is of the type found in right bundle branch block. The splitting was independent of respiration. Note the relatively faint sounds of the ventricular extrasystole and the readily heard third heart sound at the apex. The heart rate of 40 suggests complete heart block but the absence of variation in loudness of the first sound makes this pattern compatible with sinus bradycardia, partial heart block with dropped beats, or a rare combination which occurred in this case, complete heart block with atrial fibrillation.

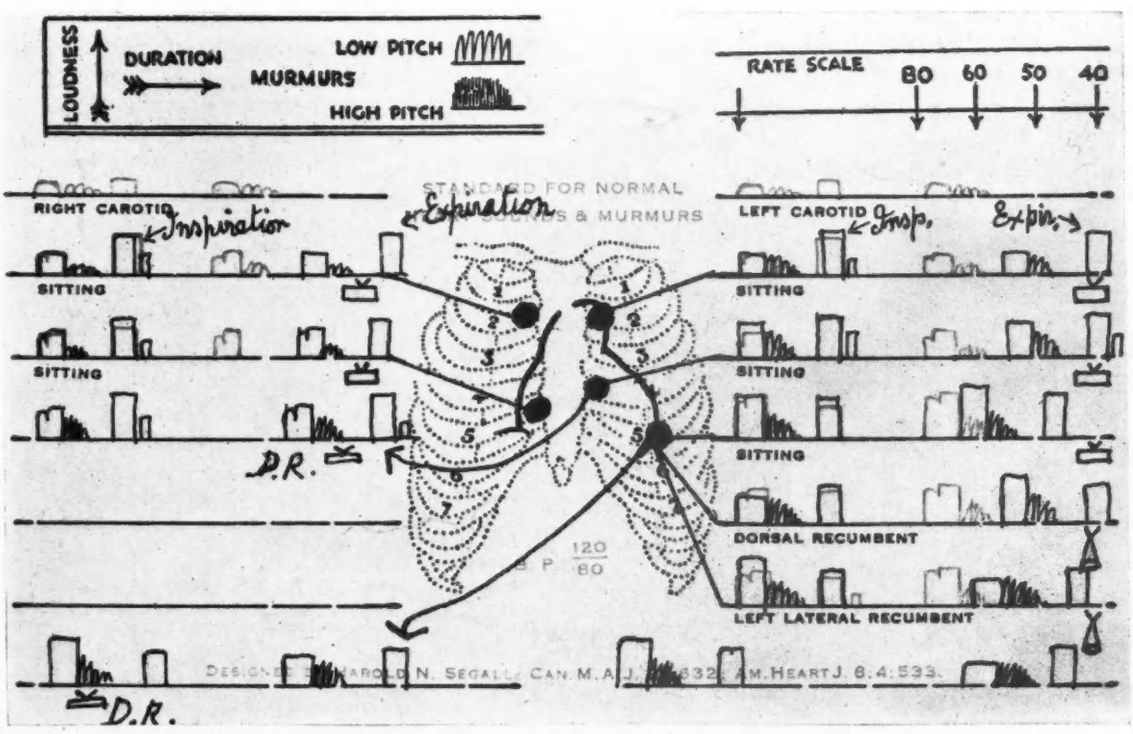

Fig. 11.—(Joseph W., Jr.) The electrocardiogram recorded on September 17, 1956, appears in Fig. 5. There is a short, coarse systolic murmur immediately after the first sound which might mask a split first sound of the type associated with right bundle branch block. No such splitting of the first sound could be detected anywhere. However, the second sound, at both borders of the sternum, readily revealed the splitting that is typical of right bundle branch block. The second component of the second sound was somewhat louder during inspiration than during expiration along the left border of the sternum. The variations in loudness of the first sound are associated with the variations in F-R intervals during atrial flutter. The variations in loudness of the first sound were best identified at the apex.

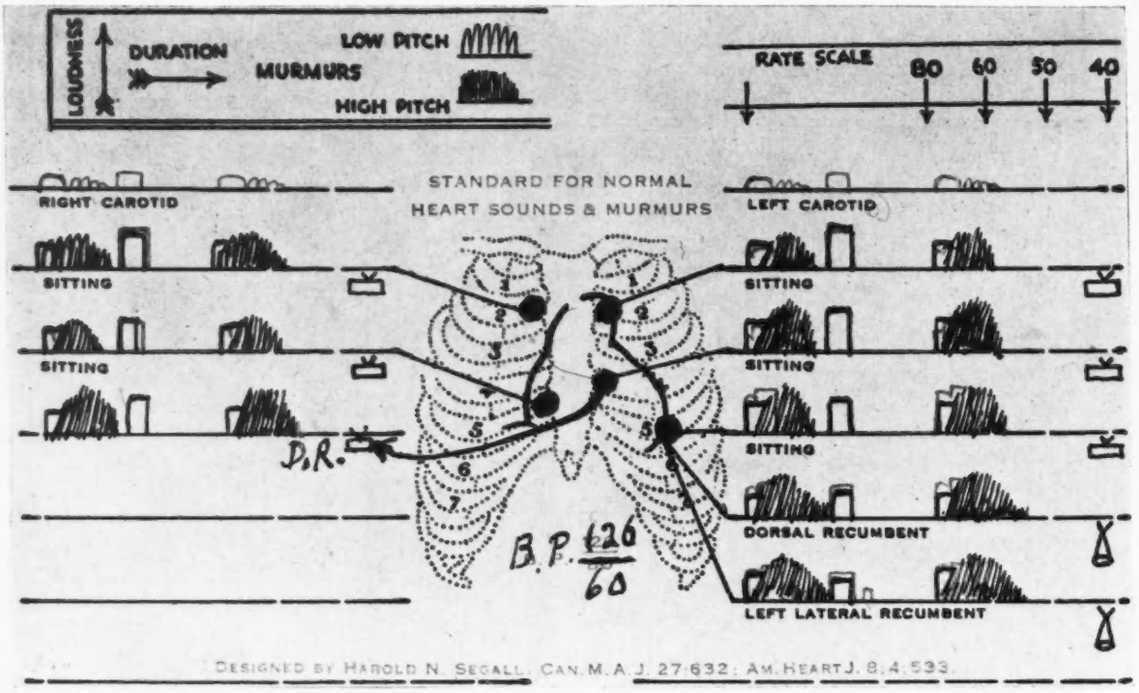

Fig. 12.—(Mrs. Alberta B.) This pattern of heart sounds was recorded on the same occasion as the electrocardiogram shown in Fig. 6. The second sound is about normal in loudness and perhaps a little shorter than normal along the right border of the sternum and at the apex. The first sound is everywhere almost entirely masked by a loud systolic murmur, which has a dominant coarse quality at the aortic and pulmonic areas and a dominant blowing quality at the left border of the sternum near the fourth intercostal space and at the apex. No third sound or diastolic murmur was detected anywhere. The point of maximum loudness is in the vicinity of the fourth left intercostal space, near the sternum, but the systolic murmur is only slightly less loud at other areas. This murmur was interpreted as compatible with an interventricular septal defect.

lasted a few seconds. Because of nervous instability she was referred for psychiatric therapy. She benefited considerably, and has continued her visits to the clinic since October 1960. She has continued on isoproterenol HCl (Isuprel) therapy during and after her stay in hospital in doses of 15 mg. every two hours.

The youngest son, Gilbert, who works as a pullman car porter, is in good health. He was born in 1931 and could recall only one illness, pneumonia

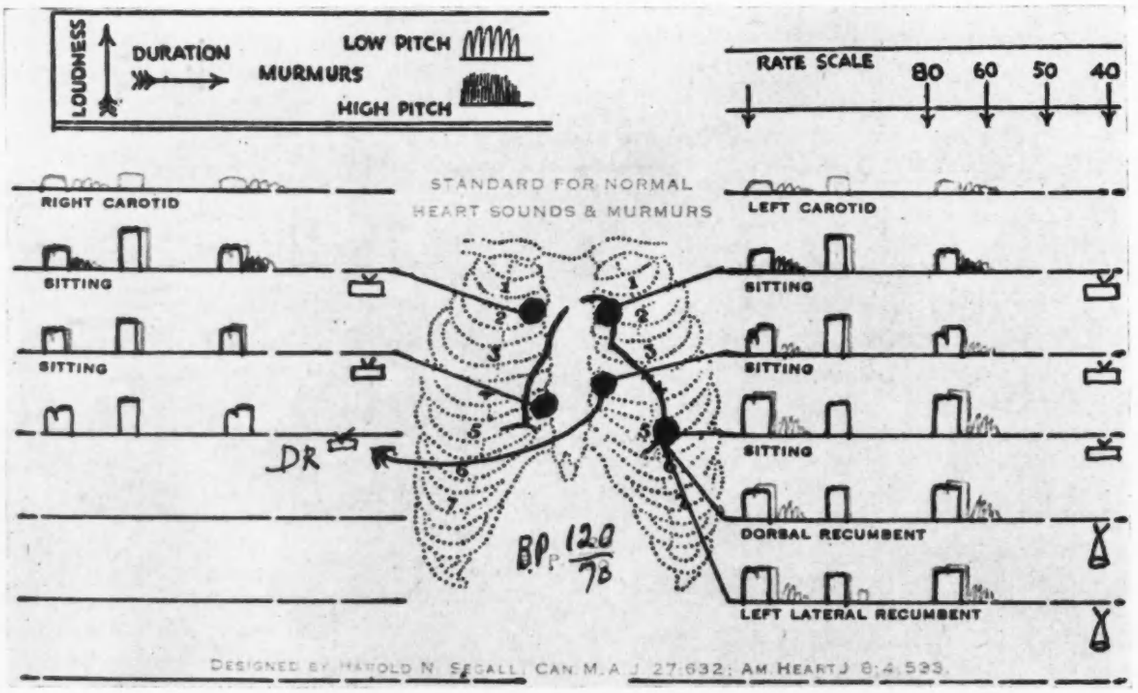

Fig. 13.—(Gilbert W.) This pattern of sounds was recorded on the same occasion as the electrocardiogram shown in Fig. 7. There was Wolff-Parkinson-White syndrome with a P-R interval of 0.12 sec. It is noteworthy that the pattern of heart sounds is normal in all respects. The first sound was not unusually loud at any area. No evidence of valvular disease could be detected. There is nothing particularly characteristic of the sounds in a case of Wolff-Parkinson-White syndrome.

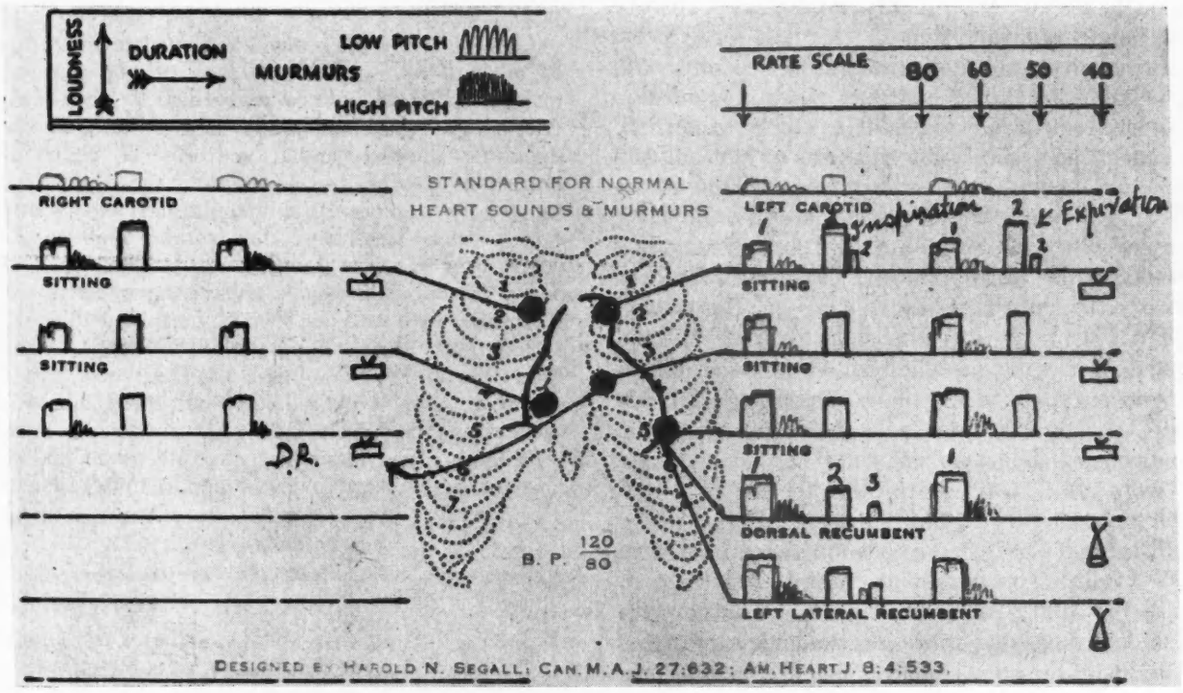

Fig. 14.—(Jean-Pierre W.) The heart sounds shown in this illustration were recorded on the same occasion as the electrocardiogram shown in Fig. 8. There was Wolff-Parkinson-White syndrome with a P-R interval of 0.12 sec. The pattern of heart sounds is within the range of normal. The splitting of the second sound at the pulmonic area is of the type often found in normal young people. The second component is a faint, short, sharp sound which is separated from the first component by a very short interval of time and tends to be somewhat louder during inspiration than during expiration. The systolic murmur is of the physiologic type. This pattern of sounds reveals nothing that can be identified as particularly characteristic of Wolff-Parkinson-White syndrome. Although the first sound is somewhat louder than in the case of Gilbert W., it is still within the range of normal.

in 1951. He married at the age of 20; his wife and two children are in good health. Physical examination revealed no suggestion of Negro ancestry. His weight was 150 lb. and his height, 6′ 3¼″. Heart sounds were normal (Fig. 13). His arterial pressure was 120 mm. Hg systolic and 70 diastolic. The electrocardiogram (Fig. 7) showed sinus rhythm with typical Wolff-Parkinson-White pattern. He has not experienced palpitation to suggest that he might have had paroxysmal tachycardia.

Jean-Pierre was born in 1928 and was said to have tuberculous glands in the neck as a baby of 18 months. He grew up to be a healthy, strong labourer, 6′ ¼″ tall and weighing 220 lb. He could recall no illnesses and had no symptoms of any impairment in health. He married at the age of 21, and his wife and four children are alive and well. His heart size and sounds (Fig. 14) were within the range of normal. His arterial pressure was 150 mm. Hg systolic and 100 diastolic. The electrocardiogram (Fig. 8) presented only a minor deviation from normal but this is suggestive of the Wolff-Parkinson-White syndrome. Some facial features suggestive of Negro ancestry were noted.

A fourth son, Mathias, aged 45, revealed no suggestion of his Negro ancestry. His health was normal. His weight was 129 lb. in about 6 pounds of clothes and his height was 5 ft. 4 in. The heart size, shape and sounds were well within the range of normal. His blood pressure was 140 mm. Hg systolic and 90 diastolic. The electrocardiogram showed a P-R interval of 0.20 sec., and is regarded as within normal range.

The sixth child, a daughter in her forties who is known to have diabetes, hypertension and dizzy spells, was not available for examination. This member of the family and the children of all six siblings have yet to be studied.*

Mrs. Joseph W., Sr., aged 66 in 1955, was born of French Canadian parentage in Gaspé and was in apparent good health. Her electrocardiogram revealed a moderate degree of left axis deviation suggestive of left ventricular enlargement, sinus rhythm and a P-R interval of 0.16 to 0.18 sec. The pattern of heart sounds was well within the range of normal. Her blood pressure was 140 mm. Hg systolic and 90 diastolic.

Michel W., the son of Joseph Jr., aged 8 in 1955, revealed normal heart size and sounds, sinus rhythm and a P-R interval of 0.16 to 0.20 sec.; physiological right axis deviation and a juvenile T-wave with terminal inversion in lead V2.

DISCUSSION

We may readily imagine the etiology of these abnormalities of cardiac rhythm and conduction as congenital. Firm proof of this would require evidence that the abnormalities existed at birth, and this cannot be provided now. Indeed, for the father, hypertensive and arteriosclerotic heart disease would be an acceptable label of etiology and with some, though less justification, it might be

*This study is now in progress and will be reported by Dr. J. Blustein.

applied to his son Joseph. Rheumatic heart disease merits some consideration in the case of Alberta because of the systolic murmur. The two sons with Wolff-Parkinson-White patterns have a condition whose etiology is unknown; it has been described in infants. Congenital abnormalities of rhythm and conduction have been observed quite rarely since the advent of electrocardiography. In 1935, together with Goldbloom,[2] we observed and reported atrial fibrillation in an infant of three months who showed clinical signs of this arrhythmia at birth. This is the first case of its kind reported. Aylward[3] in 1928 described two siblings who presented a slow pulse, less than 50 per minute, shortly after birth. Aitken[4] recorded the first electrocardiograms in these children when they were about four years old and demonstrated complete heart block. Another family, reported by Wendkos and Study,[5] bears some resemblance to the W. family. The father, examined at the age of 33, had the Wolff-Parkinson-White syndrome with attacks of paroxysmal supraventricular tachycardia. One of his children, aged five years, showed complete heart block. A second child was found to have a heart rate of 50 before birth, and an electrocardiogram recorded at the age of two days showed complete heart block. This child died on the third day; autopsy revealed coarctation of the aorta with a large patent ductus arteriosus. Histological studies failed to identify the bundle of His, which is also difficult to find in the hearts of normal infants. More recently, DeForest[6] reported familial tendency to left bundle branch block: a mother, two of her six children, a son and a daughter, and the mother's brother, one of her six siblings, showed this abnormality. Only the last, a man of 65, showed any evidence of cardiovascular disease, namely, hypertension and cardiac enlargement.

The possibility that Joseph W. Sr. presented the type of familial cardiomegaly described by Evans in 1949[7] cannot be ignored, although the hypertension observed when he was first seen seemed to account for his cardiac enlargement. It is noteworthy that none of his children showed evidence of cardiomegaly. Schiebler and his associates[8] recently reported two cases of familial cardiomegaly with Wolff-Parkinson-White syndrome. The two siblings in our family who showed this electrocardiographic pattern had no cardiomegaly.

In searching for the etiology of bundle branch block which comes to light unexpectedly in routine electrocardiograms, the possibility of congenital etiology should be given serious consideration. Clues can be found in recording electrocardiograms of parents, siblings and offspring. The clinical course of the father, one son and one daughter in this family suggests that right bundle branch block of congenital origin may become complicated by other disturbances in rhythm and conduction including complete A-V dissociation with Adams-Stokes syndrome.

SUMMARY

Clinical and electrocardiographic data are presented as encountered in five members of one family, who manifested abnormalities of cardiac rhythm and conduction. In this family, the father, one son and a daughter showed similar patterns of right bundle branch block and developed Adams-Stokes syndrome as well as various atrial arrhythmias and ventricular extrasystoles. The father died suddenly at age 74, 14 years after his first fainting spell. The son and the daughter continue to have recurrences of Adams-Stokes syndrome. Two sons are asymptomatic but their electrocardiograms show Wolff-Parkinson-White syndrome. Although all five were first studied when they were adults, it seemed most likely that their abnormalities were congenital. This family illustrates the need for considering the possibility of congenital etiology in cases of such disturbances of conduction and rhythm.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE TREATMENT OF SYPHILIS

It was in February, 1910, that Professor Ehrlich gave into the hands of Dr. Wechselmann the results of his 606th experiment to discover a *sterilisatio magna* for cases of syphilis. The substance has been variously named, and is now commonly known as "salvarsan". In the sixteen months which have elapsed a mass of literature has grown up about the subject, which even specialists find difficult to master. The most important publication, of course, was the monograph by Dr. Wechselmann with an introduction by Professor Ehrlich himself; but it was written in German and was not readily accessible. Now, however, a translation by Dr. Wolbarst, of New York, has been issued by the Rebman Company, to which is added a review of the literature as late as January of the present year. As an instance of the thoroughness with which the work is done we may mention that Dr. Fitzgerald's paper and the editorial article in the January issue of this *Journal* are both cited. Ehrlich himself writes the introduction, and Wechselmann gives a full consideration of the results which he obtained in fourteen hundred cases. The coloured plates are of singular beauty and illustrate most vividly the outcome of the treatment.

Another important work is " '606' in Theory and Practice", by Professor Ehrlich and J. E. R. McDonagh, F.R.C.S., the latter of whom was the first observer in England of the treatment of syphilis by "salvarsan". The book is one of the Oxford Medical Publications, and in the introduction Professor Ehrlich commends Mr. McDonagh's work in establishing the best method of administering the drug and its dosage, as well as when it should be repeated. The book, like Wechselmann's, is a practical one and is characterized by a wealth of clinical material.—Editorial, *Canadian Medical Association Journal*, 1: 549, June 1911.

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AUTOIMMUNIZATION – A POSSIBLE MECHANISM OF TISSUE INJURY* III—CLINICAL ASPECTS OF AUTOIMMUNITY (*Concluded*)

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Toronto

(c) Hematological Disorders

The existence and pathogenic potential of hetero- and iso-antibodies to red blood cells are well known[162] (e.g. blood transfusion reactions). A similar potential has been attributed to warm autoagglutinins directed against erythrocytes, leukocytes and platelets. The greatest difficulty in attempts to integrate such autoantibodies into the postulates of Witebsky[183] results from the finding that the antigens to which these antibodies react are largely non-specific. A single antibody may, for example, agglutinate all red cells, all leukocytes, all platelets or any combination of these cells.[37] Further, it may agglutinate cells of other species. Mature cells share antigenic properties with their bone marrow precursors. Another problem is the inability to reproduce autoimmune hematological diseases in the experimental animal, although autoantibodies against red cells without evidence of lysis have been produced.[97, 173]

In favour of the relationship between autoantibodies and such diseases as idiopathic thrombocytopenic purpura,[71, 153] autoimmune hemolytic anemia[33, 177] and paroxysmal cold hemoglobinuria[121] are the following points: (1) The factors are gamma globulins; (2) they can be passively transferred and produce transient disease; (3) they are often associated with other suspected autoimmune disorders; and (4) they are partially suppressed by corticosteroid therapy.

The most reasonable approach to the understanding of the problems of autoimmune mechanisms in these disorders has been propounded by Dausset.[37] He excluded those disorders in which an exogenous substance converts blood cell haptens to complete antigens, e.g. Sedormid or Pyramidon. The autoimmune group comprises those entities in which such external factors have been excluded. It has been noted above that these hematologic disorders may form part of such entities as SLE[34] which has many of the features of an autoimmune disease. It is also noteworthy that these same autoantibodies may make their appearance in such conditions as lymphomas, leukemias and multiple myelomas in which a neoplastic proliferation of immunologically competent cells may lead to maturation of "forbidden" clones with self-destroying propensities.[35, 163]

(d) Renal Diseases

Masugi's[108, 109] production of experimental nephritis by means of a heterologous anti-kidney serum (see Fig. 2 in the first instalment of this article), streptococcal-induced nephritis in animals,[50] the similarity of experimental foreign protein nephritis to the various human lesions,[136] and the presence of gamma globulin in glomeruli of both experimental and human lesions of glomerulonephritis[111, 112, 125] have all contributed to the concept that this disease in all its manifold manifestations is the result of immunologic processes.

The idea that acute glomerulonephritis may be an immunologic disorder has been generally accepted because of the possible involvement of a foreign antigenic material (streptococcal antigen) in the production of the lesions.[149] It has been suggested that the condition may be caused by a kidney-damaging antibody directed against some body constituent which has been rendered antigenic by contact with specific streptococci.[64]

Autoimmune mechanisms have been invoked mainly for the purpose of explaining the perpetuation of the lesion, i.e. the progression to chronicity. Circulating autoimmune antibodies have been demonstrated on a number of occasions.[93, 99, 171] The claim has been made by Kramer *et al.*[90] that progressive and fatal glomerulonephritis may be directly related to the persistence and a rising titre of such anti-human-kidney antibodies.

An experimental model has been produced by Hunter in rats which, upon injection of the rat's own kidney tissue with adjuvant, develop all the stigmata of the nephrotic syndrome.[79] Hess *et al.*[74] have further shown that such a nephrosis could be transferred by means of lymphoid cells.

Further, it should be pointed out that, unlike most other suspected autoimmune disorders, glomerulonephritis, both human and experimental, is predominantly a proliferative rather than a destructive process (Figs. 19 to 21). The finding of gamma globulin in glomeruli in the various forms of Bright's disease[111, 112, 125] and the demonstration of electron-dense deposits in glomeruli in various forms of glomerulonephritis which were interpreted as representing antigen-antibody complexes, or antibody alone, have suggested that circulating, rather than cell-bound autoantibodies may be responsible for or involved in the production of the lesion (Figs. 19 to 21).[118, 119, 158, 159] In this respect, glomerulonephritis differs from all other suspected autoimmune *tissue* injuries in which such circulating antibodies have been virtually excluded as direct pathogenic agents.

(e) Neurological Disorders

Morphologic and clinical similarity between experimental autoimmune lesions of the central nervous system and certain demyelinating encephalomyelitides of man suggest that an autoimmune mechanism is involved in the latter.[87] These human

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†This is the third of the three instalments in which this article has been published.

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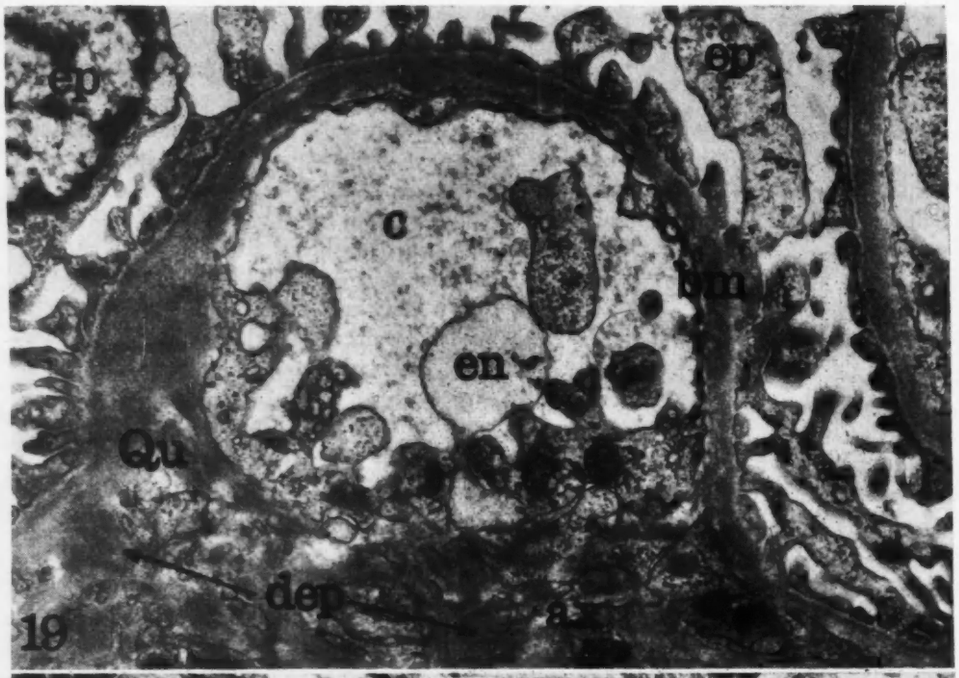
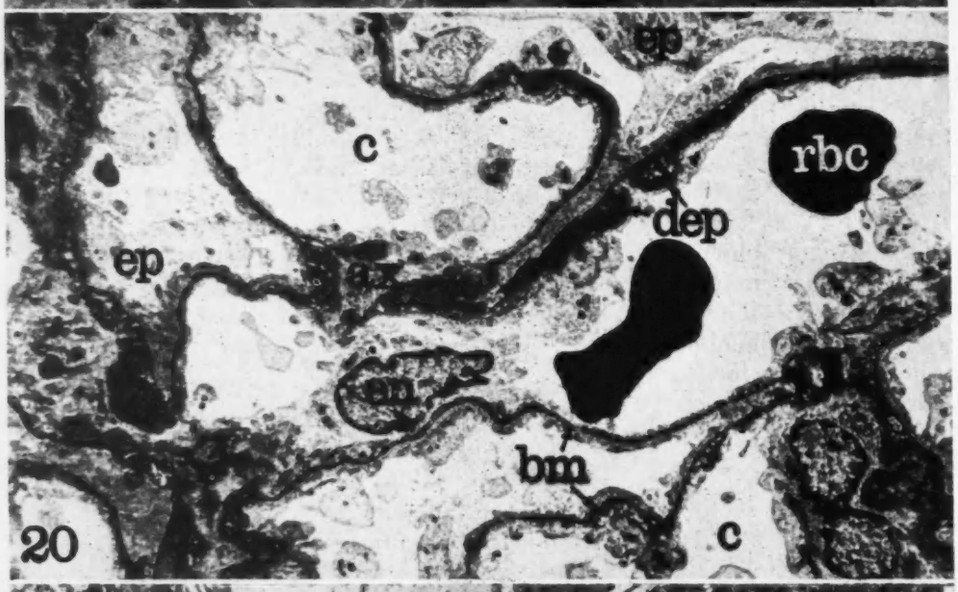
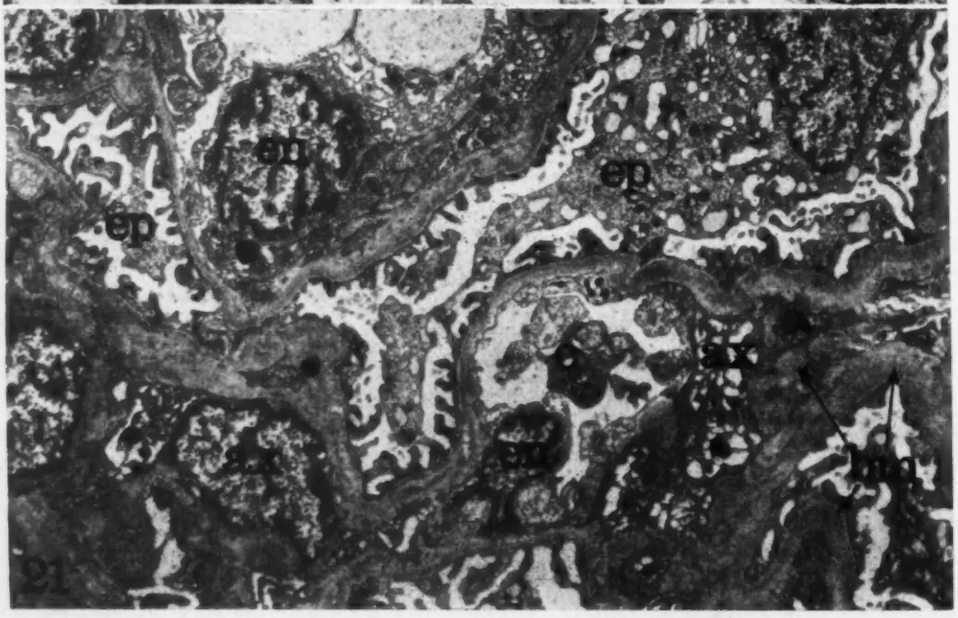






Figs. 19 to 21.—These electron micrographs illustrate three phases of Bright's disease which is suspected of being an autoimmune lesion. They differ from such lesions in other organs by the absence of immunologically competent cells in glomeruli and by their essentially proliferative rather than destructive character.

Fig. 19.—Glomerular capillary from a case of acute glomerulonephritis. The lumen is narrowed by hyperplastic endothelial cells and the basement membrane is diffusely swollen and irregular in thickness. This process, designated as Quellung, is thought to be caused by imbibition of circulating complexes of antigen and antibody by the basement membrane. Deposits of a similar material are present in the axial region of the glomerulus. Osmium tetroxide and protargol, × 11,760.

Fig. 20.—Glomerular capillaries from a child with lipoid nephrosis. The lumina are widely patent. The basement membranes are variably thickened owing to deposition of an electron-dense material abutting on to them as well as a result of a more diffuse and irregular Quellung. Osmium tetroxide and periodic acid-silver methenamine, × 2700.

Fig. 21.—Almost totally occluded capillaries in a practically obsolete glomerulus from a case of chronic glomerulonephritis. The capillary narrowing is thought to be due partly to an irregular diffuse Quellung of the basement membrane and polymerization of previously deposited circulating complexes of antigen and antibody together with a marked endothelial hypertrophy and hyperplasia. An increase of a basement membrane material in the axial regions of glomeruli causes further constriction of the capillary lumina. Osmium tetroxide and protargol, × 4220.

(ep- epithelium; c- glomerular capillary; bm- basement membrane; en- endothelium; ax- axial (mesangial) region of glomerulus; dep- deposits of material suspected of representing antigen-antibody complexes; Qu- Quellung of basement membrane; rbc- red blood cell.)

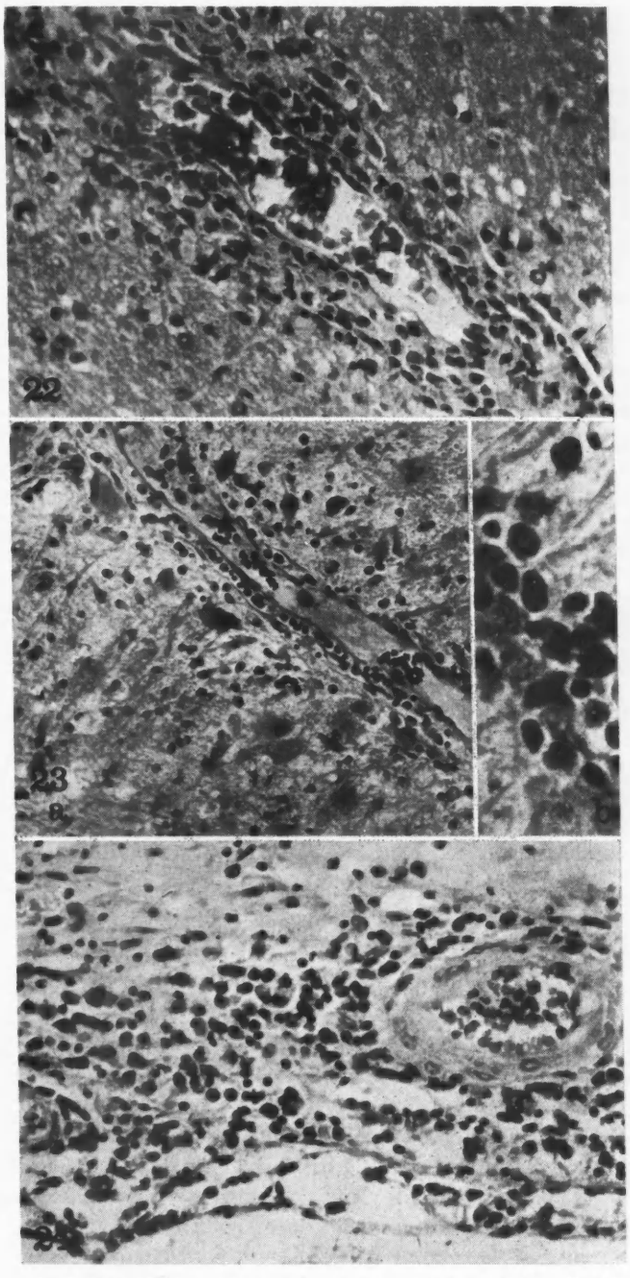
pathologic entities may be divided into two morphologic types:[131] (1) perivenous diffuse encephalomyelitis, including post-vaccinal and serogenetic (e.g. tetanus, diphtheria, etc.) encephalomyelitis and para-infectious encephalomyelitides occurring in the course of acute viral infections; (2) focal sclerosing encephalomyelitis including acute necrotizing encephalomyelitis, neuromyelitis optica, multiple sclerosis and concentric sclerosis.

The clinical evidence that these diseases may have an autoimmune etiology is rather scanty. Anti-brain autoantibodies have been demonstrated in multiple sclerosis and some other diseases of the central nervous system.[2, 42, 154] Because of the curious uniformity in the character and in the time of onset of human postinfectious encephalomyelitis its immunologic nature has been suspected.[63] Such considerations included post-rabic vaccinal encephalomyelitis and led to the inclusion of multiple sclerosis in the group when it was shown that in Japan these two diseases were strikingly similar in character.[167]

The common morphologic denominator of the previously mentioned diseases in man and of the experimentally produced encephalomyelitis is demyelination. Paterson[129] has stated that demyelination is never a primary histologic change. A variety of noxious stimuli may cause perivascular demyelination and he suggested that in the experimental lesion it is probably secondary to vessel injury and ischemia. However, the subsequent successful transfer of the experimental disease by Paterson[130] from a sensitized animal to a normal recipient animal by means of lymphoid cells suggested that these immunologically competent cells may have a more direct causative role in the morphogenesis of the lesions.[176]

The presence of collections of immunologically competent cells in the central nervous system, often in perivenous locations, is open to a number of interpretations. In the experimental autoimmune lesion (Fig. 22) they are thought to be directly injurious to brain tissue.[176] Similar cells (particularly plasma cells) were found in the brain of an individual who received Co^{60} (gamma) radiation (Fig. 23). In this instance the cells were interpreted as representing a reaction to released antigens of brain tissue secondary to the radiation injury.[92] This is somewhat similar to the clinical interpretation of thyroid autoantibodies developing after I^{131} therapy for hyperthyroidism. A plasma cellular meningitis has been noted in association with rheumatoid disease (Fig. 24) in which the presence of these cells in the subarachnoid space was also thought to be secondary to a release of an unknown antigen.[155] Thus, neither the presence of demyelination nor the infiltration and/or proliferation of i.c.c.'s can be considered *specific* evidence of a primary autodestructive disorder in the central nervous system.

Despite these considerations the morphologic and clinical similarities of the human and experimental diseases outlined above cannot be ignored and an immunopathologic process cannot at present be excluded as a cause of these human diseases.



Figs. 22 to 24.—The variable interpretation of the significance of immunologically competent cells in the central nervous system is illustrated in these photomicrographs.

Fig. 22.—Perivascular proliferation of immunologically competent cells in the white matter of a guinea pig injected with its own brain homogenate in adjuvant. The cells here are thought to possess autoaggressive propensities. H. and E., × 297.

Fig. 23.—Perivascular proliferation of immunologically competent cells with many plasma cells (magnified in Fig. 23b) in an area of demyelination caused by Co^{60} (gamma) radiation. The cells here were thought to represent a response to the release of antigenic materials from brain tissue. They were clearly not responsible for the destruction of brain tissue. H. and E., Fig. 23a, × 256; Fig. 23b, × 817. (Courtesy of Dr. P. Lampert.)

Fig. 24.—Perivascular proliferation of immunologically competent cells, predominantly plasma cells in the subarachnoid space of a case of systemic rheumatoid disease. Their presence here was thought to be caused by a release of an unknown antigen from destructive rheumatoid nodules in the dura mater. H. and E., × 377.

(f) LIVER DISEASE

Attempts to produce experimental autoimmune liver injury have so far uniformly failed, although isoimmune liver injury has been produced (see Fig. 1 in the first instalment of this article).[108] It may be that the close contact of the liver with the RE system during embryogenesis and in postnatal life makes it extremely difficult to breach the barrier of immunologic tolerance.

Gear[60] was the first to suggest the implication of autoimmune mechanisms in liver disease when he demonstrated that the yellow fever virus renders liver constituents antigenic. Precipitins which reacted with human liver extracts were demonstrated in sera of patients convalescing from homologous serum jaundice following yellow fever vaccination.[78]

Gajdusek[58, 59, 104] showed that the sera of patients with SLE, lupoid hepatitis and macroglobulinemia contained complement-fixing antibodies against liver tissues. However, even in cases with high titres such antibodies failed to react with the patient's *own* liver tissue.[101, 102] A basic requirement for an autoclastic pathogenesis was therefore lacking. A subsequent study, however, showed that such true complement-fixing autoantibodies could be demonstrated in some sera.[105, 170, 171] Vorlaender[170, 171] was able to produce complement-fixing anti-liver autoantibodies in rabbits by injecting them with saline suspensions of liver tissue in adjuvant. These phenomena confirm the existence of immunologic changes during the course of liver disease.

High titres of anti-liver autoantibodies were found in a case of primary biliary cirrhosis.[103] Autoantibodies to other tissues were also present. On the other hand, no gamma globulin fixation could be demonstrated in the liver of patients with this disease.[29] Cameron[24] suggested that Hanot's cirrhosis may be an expression of local immunity because of the prominent collections of lymphocytes found in the liver. Hamilton[70] was able to demonstrate the presence of hematoxylin bodies in primary biliary cirrhosis in support of an autoimmune etiology.

It has been suggested that many cases of hepatic cirhosis of cryptogenic origin may have a hyperimmune basis.[123] Klatskin[88] went so far as to state that such a process may be the "other and as yet unidentified mechanism" involved in the pathogenesis of Laennec's cirrhosis.

It is generally accepted that complement-fixing anti-liver autoantibodies may be a valuable index of activity of a liver disease.[65] One must, however, always keep in mind the finding of a natural antibody in human serum which reacts *in vitro* with constituents of many tissues, including liver.[86, 124] Olitzki and Bernkopf also showed that the sera of patients with infectious hepatitis in a high percentage of instances gave a positive precipitin reaction with cholesterolized extracts of liver tissue. However, a substantial number of normal sera also gave a similar result. It is therefore imperative that positive anti-liver serologic tests be interpreted with caution.

SUMMARY

Autoimmunization as a response of the body to autoantigens can no longer be doubted. Whatever the modes which lead to the change of an autologous tissue component to a full antigen, it is now clear that the antibody-producing mechanisms of the body can respond to their release by the production of circulating autoantibodies. Such antigen-centred concepts have been recently superseded by the view, based on Burnet's clonal selection theory, that cells of the reticuloendothelial system may undergo fundamental changes (somatic mutations) leading to failure of self-recognition. In this instance, too, the production of circulating autoantibody could result.

The experimental immunopathologist has produced a series of models of autoimmune diseases which are evidenced in tissues by destruction of the target organ parenchyma associated with an infiltration of immunologically competent cells. Since these diseases could not be transferred to healthy recipients by means of circulating antibody, but could be induced by transfer of lymphoid cells, the conclusion would appear justified that the experimental prototypes were due to self-destructive activity of these cells. Such a concept remains highly speculative.

The pathologist possesses no definite criteria for the morphologic diagnosis of autoimmune lesions. Guided by the principle that morphologic similarity of lesions does not necessarily imply identical or similar pathogenesis, he is reluctant to accept the presence of tissue destruction and of immunologically competent cells in a lesion as necessarily implying autodestruction.

The clinician has come to realize that circulating autoantibodies may have at least two meanings. In some circumstances they are obviously a *reaction* to tissue injury, e.g. anti-heart antibodies after myocardial infarction. In others, the possibility cannot be denied that they may be related to the presence of a truly self-destructive process.

In general, the entire evidence for the existence of human autoimmune diseases is largely circumstantial. The eagerness of the clinician to determine the significance of autoantibodies, and of the immunologist to explore the mechanisms of autoimmunization have led to an impasse, since the pathologist has been unable to supply the necessary information which would permit the formulation of a concrete concept of autodestructive disorders.

At present the concept of autodestruction has served as a manifold stimulus to thought and research, and it can only be hoped that the concerted efforts of clinicians, immunologists and pathologists will in due course clarify the problems at hand.

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A SURVEY OF POSTOPERATIVE INFECTION ON A GYNECOLOGICAL SERVICE*

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THIS IS a report of a study undertaken to determine the pattern of infection acquired during and after gynecological surgery performed at the Vancouver General Hospital. It is concerned with the incidence and the site of such infections, the causative organisms and the role played by antibacterial therapy.

Two hundred and seventy-two patients were followed up postoperatively. These operations included 52 abdominal procedures, 50 anterior-posterior vaginal repairs including 12 with amputation of the cervix, 50 vaginal hysterectomies with repair and 96 minor vaginal procedures. The latter was made up mainly of dilatation and curettage. In addition, there were 25 cases of radium insertion. All patients were regarded as non-infected prior to surgery and in each type of procedure consecutive patients were studied. With one or two exceptions, all major operations and approximately one-half of the minor procedures were performed by gynecologists or members of the resident staff.

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The major types of infection following gynecological surgery are: (1) pelvic cellulitis, which may spread laterally from a uterus *in situ* or may affect the cellular tissues of the pelvis following hysterectomy; (2) vaginal vault infection, which is a wound infection at the site of removal of a uterus; and (3) urinary tract infections.

The development of pelvic cellulitis, either from lymphatic spread of organisms from the genital tract, or by actual contamination through the open vaginal cuff after abdominal hysterectomy, is common. In vaginal operative procedures, such as vaginal plastic operations, or vaginal hysterectomy with repair, infection deep to the vaginal wall flaps may lead to cellulitis or the loculation of purulent material. Hematoma formation favours this development. Urinary tract infections are frequent, and because gynecological surgery is associated with some risk of minor trauma to the urinary tract, the problem of temporarily disturbed bladder function and stasis is a major factor in etiology.

In order to be as objective as possible the following criteria were established to classify infections:

1. The presence of the classical signs of infection, i.e. pain, heat, swelling, redness.

2. Temperature elevation to level of morbidity 100.4° F. for two consecutive days, excluding the first 24 hours after operation.

3. The presence of purulent or foul discharge or the culturing of pathogenic organisms.

4. Disruption of a wound.

Those patients who, in their postoperative course, exhibited any three of these signs were classified as being infected.

Urinary tract infections were classified separately and, in the main, were manifested in the form of cystitis. These were recognized by the presence of pus in urine, or the growth of a pathogenic organism on urine culture, and the symptoms of dysuria or frequency.

TABLE I.—INCIDENCE OF POSTOPERATIVE INFECTIONS

Procedure	*No. of cases*	*Surgical infections*		*Urinary infections*	
		Number	*%*	*Number*	*%*
Vaginal hysterectomy with repair	50	17	34%	26	52%
Vaginal repairs	50	2	4%	17	34%
Abdominal procedures	51	7	14%	9	18%
Minor vaginal procedures	96	2	2%	1	1%
Radium insertions	25	1	4%	0	0
Total	272	29	11%	53	20%

Table I shows that 17 of the 50 patients with vaginal hysterectomies and repairs had infections. The most severe of these was a 46-year-old woman, gravida IV, para I, with a rather marked cystocele and rectocele. Her postoperative course was uneventful until the seventh day, when she developed severe lower abdominal pains, tenderness, distension, signs of peritoneal irritation and temperature elevation to 101° F. She had a foul vaginal discharge, with induration in the right parametrial area. This responded to administration of antibiotics but subsequently the patient developed a pulmonary embolism. On her 40th postoperative day she suddenly passed about 300 c.c. of purulent material per vaginam. Following this her recovery was uneventful.

In contrast to this patient's course, the remainder of these infected vaginal cases most commonly exhibited an uneventful course for one or two days postoperatively, and then developed temperatures to 101-103° F., lower abdominal pains, tenderness and foul discharge, the process resolving after three to six days of antibiotic therapy.

In the vaginal hysterectomy and repair group, 26 (or more than one-half) had a urinary tract infection. Of those with vaginal repairs without hysterectomy, only two had severe infection and 17 of 50 had cystitis. In this series the patients with vaginal plastic procedures had considerably less morbidity than when hysterectomy was combined with a plastic procedure.

There were seven infections following abdominal operations. Of these, three had abdominal wound infections with partial disruption and purulent discharge. Two patients had vault infections, one had combined vault and abdominal wound infection, and one had a vault infection with septicemia. In this group there were nine urinary tract infections.

The operation of dilatation and curettage is usually regarded as an innocuous procedure but, of 84 patients, two had infections subsequent to dilatation and curettage performed for menorrhagia. In one of these the infection was manifested as a parametritis and in the second as an abscess in the posterior cul-de-sac. One case of radium insertion resulted in severe parametritis.

Table II shows that in the majority of infected cases the coliform group of organisms was involved. Twelve of 19 cultures of infections in vaginal repairs and vaginal repair with hysterectomy grew one of these organisms and three of seven infections after abdominal surgery were of the coliform type. One patient with an abdominal hysterectomy developed a Bacteroides septicemia with an associated Proteus vault infection. The only *Staphylococcus aureus* infection occurred in the incision after removal of a dermoid cyst of the ovary.

The cultures of vaginal discharge in the two patients with infections after dilatation and curettage did not help in identifying the organism involved.

On the night prior to operation, in 18 cases of vaginal hysterectomy with repair, cultures were taken of every cervix. Seven of these showed positive cultures, of which four were coliform organisms, one an anaerobic streptococcus, one nonhemolytic staphylococcus and one diphtheroids and Lactobacillus. In the remainder there was no growth.

TABLE II.—ORGANISMS CULTURED IN INFECTIONS

Procedure	*No. infected*	*Coliform*	*Staphylococcus aureus*	*Staphylococcus albus*	*Bacteroides*	*Non-hemolytic streptococcus*	*No growth*
Major vaginal procedures..	19	12		1	1	1	4
Abdominal procedures....	7	3	1	1	1		1
Minor vaginal procedures..	2			1			1
Radium insertion.....	1	1					
Total.....	29	16 (55%)	1 (3%)	3 (11%)	2 (7%)	1 (4%)	6 (20%)

Postoperatively this group had only one major infection from *E. coli*, in a patient who preoperatively grew the same organism.

This group is too small to evaluate the role of preoperative vaginal cultures.

Table III shows that urinary tract infections were very frequent, not only after vaginal, but also after

TABLE III.—ORGANISMS CULTURED IN URINARY TRACT INFECTION

Procedure	*No. infected*	*E. coli*	*Proteus*	*Para-colon*	*Pyocyaneus*	*A. aerogenes*	*Staphylococcus albus*	*No growth*
Major vaginal procedures	43	29		2	3	2	1	6
Abdominal procedure	9	4	1	1	1	2		
Minor vaginal procedures	1	1						
Radium insertions	0							
Total	53	34 (64%)	1 (2%)	3 (6%)	4 (7%)	4 (7%)	1 (2%)	6 (11%)

abdominal surgery. Here again the major offenders were the coliform group of organisms, with a scattering of other organisms commonly implicated in urinary tract infections. Seven urine cultures were taken 24 hours prior to major vaginal procedures. Of these, one grew *E. coli* and the other six showed no growth. Postoperatively, only one of these seven remained sterile on culture.

In these days when prophylactic antibiotics are being condemned, it is interesting to note how frequently antibiotics were used on surgical patients. In major vaginal procedures, antibiotics or sulfonamides were used in 68 of 100 cases. As shown in Table IV, one-half of this number received chloramphenicol.

TABLE IV.—USE OF ANTIBIOTICS AND SULFONAMIDE DRUGS

Procedure	*No.*	*Chloramphenicol*	*Tetracycline*	*Penicillin*	*Streptomycin*	*Sulfonamide*	*Erythromycin*	*No antibiotic or sulfonamide*
Major vaginal procedures	100	34	3	7	7	48	1	32
Abdominal procedures	51	17	2	8	6	3	0	21
Minor vaginal procedures	96	10	1	10	8	1	0	75
Radium insertions	25	0	0	1	1	0	0	24
Total	272	61	6	26	22	52	1	152

Surprisingly, 59% of the abdominal surgery patients received antibacterial therapy and 25% of those undergoing a minor vaginal procedure received antibiotics. It is of interest that only one of the patients having radium insertions received antibiotics.

Of 272 patients operated upon, 44% received antibiotic therapy, and chloramphenicol was the antibiotic of choice in almost one-half of the cases receiving such therapy.

It is of interest that in the Vancouver General Hospital there have been 12 well-documented cases of aplastic anemia attributed to chloramphenicol in the past 10 years,[3, 4] with nine fatalities. However, none of these were on the gynecology service.

The incidence of infection is reflected in the average hospital stay for these surgical cases. Patients with vaginal hysterectomies averaged 17.7 days' stay with a median of 16 days; those with vaginal plastic operations, 14.2 days with a median of 13 days; those with abdominal surgery, 16.7 days with a median of 13 days; and those with dilatation and curettage, 3.5 days with a median of 3 days.

SUMMARY

1. Two hundred and forty-seven patients having gynecological surgery and 25 patients with radium insertions were followed up postoperatively for evidence of infection.

2. Criteria for classification of infection are set forth.

3. The incidence of infection following major gynecological surgery was 17% of 151 cases. The incidence following minor gynecological surgery was 2% of 121 cases.

4. The coliform group of organisms was present in over 50% of all major infections.

5. The median hospital stay for patients with vaginal hysterectomies with repair was 16 days; for those with vaginal plastic procedures, 13 days; for those with major abdominal procedures, 13 days; and for patients subjected to dilatation and curettage, 3 days.

6. Of 272 gynecological surgical patients, 44% received antibiotics or sulfonamides postoperatively.

CONCLUSIONS

Although this is a small group of patients, the findings confirm an impression that the postoperative infection rate on the gynecology service at the Vancouver General Hospital is high. The organisms of the coliform group predominate as the infecting agent. The *Staphylococcus aureus* group does not present a major problem.

Prophylactic antibiotic drugs were commonly given. Chloramphenicol was frequently used for this purpose.[5]

A rigid reappraisal of preoperative preparation, surgical technique and postoperative surgical and nursing techniques is clearly indicated. The merit of prophylactic use of antibiotics should be reevaluated.

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HEMORRHAGE FROM PEPTIC ULCER*

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DESPITE the remarkable advances in surgical, anesthetic, and blood transfusion techniques, controversy still exists concerning the treatment of patients with bleeding peptic ulcer. There are some reports of series of patients treated entirely medically,[2, 5] and others of groups of patients treated entirely surgically,[3] but most authors agree that a proportion of bleeding ulcer patients require operation.[1, 4, 9] Our aim in the operative management of this complication is the arrest of hemorrhage, safe removal of the ulcer, and partial gastrectomy. We have conducted a review to determine if there are any features in the clinical course of these patients that might assist in predicting the prognosis, the risk of further hemorrhage, the need for emergency operation, and the results of treatment.

CASE MATERIAL

In the 10-year period 1949 to 1959 inclusive, 174 patients were treated for bleeding peptic ulcer at the Wellesley Hospital, Toronto. Some of these patients had multiple admissions for hemorrhage, but these admissions are not considered separately. We have restricted our study to those cases of peptic ulcer proven by radiography, endoscopy or direct vision; other gastrointestinal conditions that might possibly lead to bleeding have been excluded. We have included cases of hemorrhage only where there have been reliable witnesses to describe a significant loss of blood through hematemesis or melena. In this review we were able to obtain information on 131 patients whose follow-up period ranged from two to 10 years. This information was obtained by personal interview of 90 patients, and by questionnaire in 41 cases.

CLINICAL FEATURES

The severity of bleeding was classified as mild, moderately severe, or severe. The hemorrhage was regarded as mild when the hemoglobin level did not fall below 11 g. % and when not more than 500 ml. of blood was required to restore the blood volume.[7] There were 60 of these patients. The hemorrhage was regarded as moderately severe when there was hematemesis or melena accompanied by syncope or shock, when the hemoglobin was between 7.5 g. and 11 g. % and when 1000 to 2000 ml. of blood was required to restore the blood volume. There were 80 of these patients. The hemorrhage was classified as severe when there was shock or syncope, when the hemoglobin was less than 7.5 g. % and when more than 2000 ml. of blood was required to restore the blood volume. There were 34 of these patients.

TABLE I.—SITE OF ULCERATION

Duodenal		141
Male	113	
Female	28	
Gastric		28
Male	18	
Female	10	
Combined		1
Stomal		3
Esophageal		1
		174

The site of ulceration and sex distribution of patients are given in Table I. There were 136 (78%) men and 38 (22%) women in the group.

A history of proven peptic ulcer or significant dyspepsia was given by 154 patients on admission. The history led one to regard peptic ulceration as the most likely source of hemorrhage, and usually led to the postponement of radiographic examination or endoscopy until bleeding had ceased.

Because of the interest in ABO blood groups in patients with an ulcer diathesis,[4] their significance was assessed in relation to the site of ulceration. Of 101 patients with duodenal ulcer 63 had type O blood (63%); this is significantly greater than the expected incidence. There were 23 patients with benign gastric ulcer and 7 of these had type A blood (39%).*

Forty-three patients had a history of more than one hemorrhage. From a review of the time intervals concerned, it was apparent that recurrent hemorrhage most commonly occurred at intervals of one to two years.

The age distribution and the mortality by decades are given in Table II.

TABLE II.—AGE AND MORTALITY

Age	*Number of patients*	*Deaths in hospital*
- 30	26	0
30 - 39	25	1 (4.0%)
40 - 49	25	1 (4.0%)
50 - 59	40	1 (2.4%)
60 - 69	2	2 (6.5%)
70+	29	7 (34.1%)
Overall mortality		6.8%

35.5% of patients were older than 60 years.

MEDICAL TREATMENT

Initially all of the patients in this study were treated medically with bed rest and the replacement of blood loss. As part of the investigation, laboratory tests were taken to exclude hemorrhagic and liver diseases. Most of the patients had gastric aspiration to assist in assessing recurrent or continuing hemorrhage. The decision to undertake emergency operation was made if the patient had

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*Dr. Brian Moore of the Red Cross Transfusion Service of Toronto found in a random sample of 14,500 blood donors that type O formed 46.04% of the group, and type A 39.62%.

TABLE III.—MORTALITY AMONG 140 MEDICALLY TREATED PATIENTS

Massive hemorrhage	1
Arteriosclerotic heart disease	3
Emphysema	1
Cerebral vascular disease	1
Portal cirrhosis	1
	7 (5%)

not stopped bleeding after 24 to 48 hours of constant observation. Other factors were also taken into consideration, and will be discussed later.

The hospital medical mortality is explained in Table III.

PROGNOSIS OF PATIENTS ON MEDICAL TREATMENT (See Table IV)

TABLE IV.—RESULTS OF MEDICAL TREATMENT AMONG 95 PATIENTS WHO LEFT HOSPITAL

24 lost to follow-up	
22 died at home	
Cardiovascular	10
Undetermined	7
Pneumonia	2
Carcinoma—stomach 1, other 2	3
49 alive	
Asymptomatic	7
Further bleeding (6 required operation)	15
Further pain	23
Gastrectomy (for other than bleeding)	4

It should be noted that only seven of 49 patients were asymptomatic during the follow-up period. It is also notable that recurrent hemorrhage from peptic ulcer is common among those who have been discharged from hospital after medical treatment of peptic ulcer hemorrhage.

SURGICAL TREATMENT

Emergency operation was necessary for 34 patients (22%). The decision to undertake emergency operation to arrest hemorrhage was based on a synthesis of a large number of variable factors. Operation was performed on those patients who were judged likely to continue to bleed, and who were considered able to tolerate anesthesia and the trauma of operation. When operation was necessary, one seldom waited beyond 48 hours, and in most instances the decision had been made by the time 24 hours had elapsed. In the broadest terms the reasons for operation were: (1) Exsanguinating hemorrhage: such bleeding was uncommon, but when it occurred it was necessary to operate within a few hours of admission, i.e. by the time 3-6 litres of blood had been transfused. (2) Bleeding persisting after 24 hours of medical treatment: the need of 3-6 litres of blood in a 24-hour period is evidence of unremitting hemorrhage. (3) Recurrence, during the patient's hospitalization, of bleeding that had previously stopped on medical management. (4) Slow but persistent bleeding over a period of several days: a requirement of 500 ml. of blood every 24-48 hours indicated need for operation.

Certain other factors influenced the selection of patients for emergency operation. Shortage of donor blood was not a problem in any of the cases in this series, but such a situation is recognized as a valid reason for early operation. A previous history of ulcer hemorrhage or proven gastric ulcer was a further reason favouring a decision to operate. Conservative management was preferred for those under 35 years of age, since continuing or recurrent bleeding is tolerated better by these patients than by the aged. When a patient had an associated disease, it did not alter the criteria for emergency operation unless the disease was so serious in itself as to be a threat to life, or unless the patient was decrepit.

As a general rule we prefer not to operate unless the source of hemorrhage is known. A barium examination of the esophagus, stomach and duodenum was performed as soon as there was a lull in the bleeding and the blood volume had been restored. It is not always prudent or feasible to submit a severely bleeding patient to the discomfort of this procedure. For this reason it was necessary to operate on several occasions without knowledge of the source of hemorrhage aside from that provided by clinical features indicating that bleeding was originating from a peptic ulcer.

In reviewing this group of patients, factors were sought which might have some influence on the need for emergency operation. Age played a minor role in determining the need for immediate or early operation; of the 52 patients less than 40 years of age, 9 (17%) required operation as an emergency, while among the 95 patients 40-60 years of age, 23 (24%) required emergency operation (1 in 6 as compared to 1 in 4). These figures are too small to be significant, but they suggest that there is little difference between these age groups in so far as their need for immediate or early operation is concerned.

The sex of the patient also had little bearing on the need for emergency operation. Eight of the 39 women required early operation (20%). Considering the site of the ulcer as well as the sex of the patient, it is noted that of 10 women with gastric ulcers, seven required emergency operation. Gastric ulcer was not such a threat in men; five of 18 men with gastric ulcers required emergency operation.

Of four patients with ulcers in the second portion of the duodenum two required operation.

The ABO blood type did not influence the need for emergency operation. Of 63 patients with type O blood, 18 (23%) required emergency operation. This was no greater than the figure for the whole group. There were 30 patients with type A blood, and 11 of these required emergency operation (29%). This figure is only slightly greater than the expected figure for the whole group.

Thirty-eight patients had elective operation at the Wellesley Hospital, either during their stay following admission for hemorrhage or at a later admission. The indications for such operations were one or more of the following: recurrent bleeding, intractable symptoms, duodenal or pyloric obstruction, or failure of healing of a gastric ulcer. Those patients requiring elective operation usually were treated medically for 10 days or more before operation was performed.

Thirty-four patients in all were operated upon as emergencies; the operation performed was, in most cases, a liberal gastrotomy and control of hemorrhage, followed by a partial gastric resection. Usually the offending ulcer was removed, but in certain cases this was not advisable because of inflammatory conditions about the duodenum. One patient, too ill for anything but a minimal life-saving procedure, was subjected to gastrotomy and control of hemorrhage by suture of the bleeding point. Partial gastrectomy was performed in the 38 elective operations. The morbidity and mortality of the 34 patients subjected to emergency surgery are given in Table V.

TABLE V.—MORBIDITY AND MORTALITY OF EMERGENCY OPERATION

Morbidity		*Deaths*
Peritonitis	1*	1
Wound infection	2	0
Duodenal fistula	3*	1
Postoperative bleeding	2	1
Wound dehiscence	2	0
Stomal obstruction	1	0
Intra-abdominal abscess	1	0
Pulmonary failure	1	1
Major skin slough (noradrenaline)	1	0
	14	4

Mortality of emergency operation: 11.7%.
*One of the patients in each of these two groups also had a major postoperative hemorrhage.
(Mortality of 38 elective operations was 2.6 (1 patient).)

Of the 72 patients who were operated upon at the Wellesley Hospital, either as emergencies or electively after the medical control of their hemorrhage, reliable follow-up information was obtained on 45. This figure therefore excludes those who died in hospital or at home, or who could not be traced. None of these 45 patients have suffered further bleeding. Results of surgery were assessed as excellent, fair or poor. An excellent result was considered as one in which the patient had no symptoms referable to the gastrointestinal tract or disabilities attributable to the operation. A slightly disabled patient was one in whom there was one or all of the following: a tendency to hypochromic anemia, failure to gain weight within 5% of the preoperative weight, or episodic or mild postgastrectomy symptoms. Subjectively these patients usually regarded their condition as excellent. A poor result was one in which the patient had one or more of the following: severe weight loss, frequent postgastrectomy symptoms of "dumping" or "bile vomiting", or continuing symptoms of dyspepsia or pain. There were 33 excellent results (73%), eight fair results (18%), and four poor results (9%).

DISCUSSION

The treatment of bleeding peptic ulcer is a team enterprise. Both physician and surgeon should see the patient soon after admission in order that later they may make an intelligent appraisal of any change in his condition. This routine is especially important in patients over 60 years of age, since it is these who have the highest mortality and incidence of associated disease. The radiologist, endoscopist and anesthetist may be called upon as the need arises.

We request an upper gastrointestinal barium examination when there is insufficient history, symptoms or signs on which to base a reliable diagnosis. The radiologist must be informed of the clinical status of the patient, and the blood volume of the patient should be restored before the examination is undertaken. The radiologists at the Wellesley Hospital, Toronto, examine these patients in the usual manner, using abdominal palpation rather than the "no touch" technique. No ill effects of this procedure have been encountered and the results therefrom have been more satisfactory than those provided by other techniques.

The endoscopist, should he be other than the consulting physician or surgeon, is requested to examine the patient when the radiological and clinical facts fail to provide a diagnosis. We have employed endoscopy immediately prior to emergency operation, when the diagnosis is in doubt but when the need for operation is clear because of severity and persistence of bleeding. We have not performed endoscopy on a sufficiently large group of actively bleeding patients to comment on this procedure as yet.

When operation is undertaken, it is advisable to locate and control the source of hemorrhage as soon as the peritoneal cavity is opened. When this has been accomplished, the operation may be completed without haste. A generous gastrotomy beginning at the pylorus is usually required; the stomach is emptied of clot and its interior is inspected.[6, 8] When bleeding has been controlled, the gastrotomy is rapidly closed and the operation continued. Technical difficulty is often encountered owing to an inflamed, edematous duodenum, as a result of which, three duodenal fistulae developed in this series. Every reasonable effort should be made to exclude the ulcer from the duodenal closure, but if for any reason this is imprudent, special care should be taken to oversew the bleeding vessel with a suture of silk or cotton. Bleeding may recur as long as three weeks after it has been arrested if this precaution is not observed. The technical problems encountered in operating on a florid, active duodenal ulcer constitute one of the major reasons for attempting to manage all such patients by medical measures initially. If these

measures are successful, and if bleeding stops, it is our practice to maintain the patient on a strict medical regimen for 10 days or more before proceeding to elective operation, should the latter be indicated.

One must expect, though not complacently, a high morbidity in those subjected to emergency operation. Wound complications are specially common. Others have also noted this and recommend the use of retention sutures in all cases.[8] The mortality of 6.8% for the entire group is not high[4, 9] but could be improved upon; two or three of the deaths in the surgical group might be regarded as due to technical errors, and it is possible to eliminate this cause of failure, thereby improving the overall mortality. In our experience the mortality rises abruptly in patients over the age of 60 years, a finding that has been reported by others.[6, 9]

The advocates of strict medical therapy will note that there is a high incidence of recurrence of symptoms in the group of patients so treated. One-third had further hemorrhage and one-half had increased pain. These facts lend support to the poor symptomatic prognosis in peptic ulcer patients followed up for a long period of time. Many had only a two-year follow-up, and it is expected that the incidence of recurrent hemorrhage will further increase with time. Indeed, since this follow-up study was completed, two patients have been admitted for hemorrhage, who at the time of their interview were without symptoms. Only one patient in seven treated by medical measures alone, had no further symptoms of peptic ulcer.

None of those who were operated upon have had further hemorrhage; this is unlike the experience of other authors.[1] No stomal ulcers have developed to date.

SUMMARY

The case records of 174 patients suffering from gross bleeding from peptic ulcer have been reviewed and a 2-year to 10-year follow-up has been carried out on 131 of these patients.

The clinical features are presented, and the treatment and its results have been discussed.

The authors gratefully acknowledge the help of the various physicians and surgeons attending the Wellesley Hospital for permission to interview their patients and review their charts; the special blood donor sampling by Dr. Brian Moore of the Red Cross Transfusion Service; and the many hours of work contributed by Mrs. Ian B. Macdonald, Mrs. Peter Warren, Mrs. W. P. Wilder and Mrs. John Stohn, in tracing these patients.

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SIMULTANEOUS SCREENING FOR MELLITURIA AND AMINOACIDURIA*

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THE chromatographic screening test for aminoaciduria[1] may be modified so that the same procedure can be used for the detection of mellituria. Since mellituria is frequently associated with aminoaciduria, the simultaneous detection of these states by a combined screening procedure is of practical value. Moreover, the chromatographic screening test for mellituria affords a higher degree of sensitivity and specificity than the Benedict's test. It also has the advantage over the glucose oxidase Uristix test because sugars other than glucose may be detected. This report describes some clinical applications of the combined screening test, a few modifications of the original technique, and an improved method for the identification of the reducing substances in urine by ascending unidirectional chromatography.

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METHODS AND MATERIAL

The technique described for screening for aminoaciduria[1] can be used for detection of mellituria, except for the last step, which is the staining procedure. At present we use Whatman 3 MM filter paper, cut in the cruciform with the aid of a plastic or film model. The centre of the paper, as well as the four application spots, can thus be marked uniformly by pencil. The length of the paper is 18.5 cm. and the width of each segment is 5 cm. (Fig. 1). Five microlitres of native urine are applied on each segment at a point 0.6 cm. from the centre as indicated by the pencil mark. To increase the sensitivity of the test, much greater volumes can be applied at each point. A tightly, diagonally rolled, 1-inch-square filter paper, Whatman No. 1, prepared with gloved hands, can be used as a wick to avoid the inconvenience of boiling a cotton twine in 10% pyridine as previously recommended.

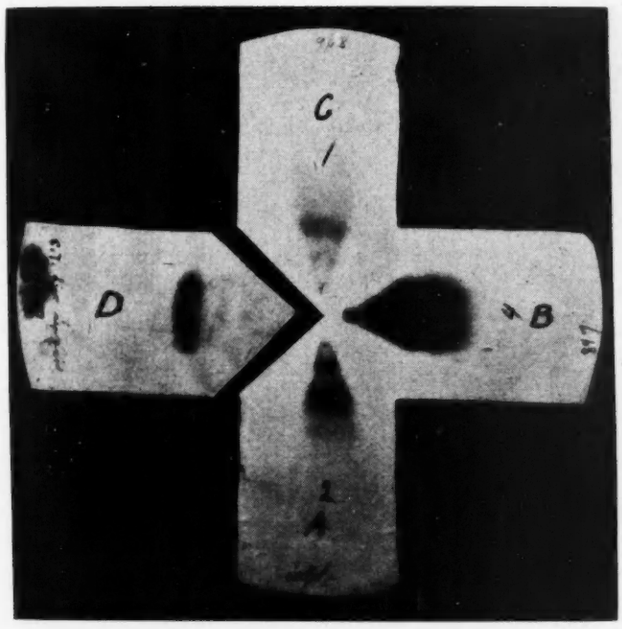

Fig. 1.—Combined screening test, using five microlitres of urine. Segment A—normal urine (control). Segments B and D—from patient No. 1. Segment C—a patient with a normal pattern. Segments A, B and C stained with ninhydrin. Note the heavy dark staining indicating a 4+ reaction for amino acids in Segment B. Segment D stained with silver oxide. Note the dark band (1+), indicating mellituria.

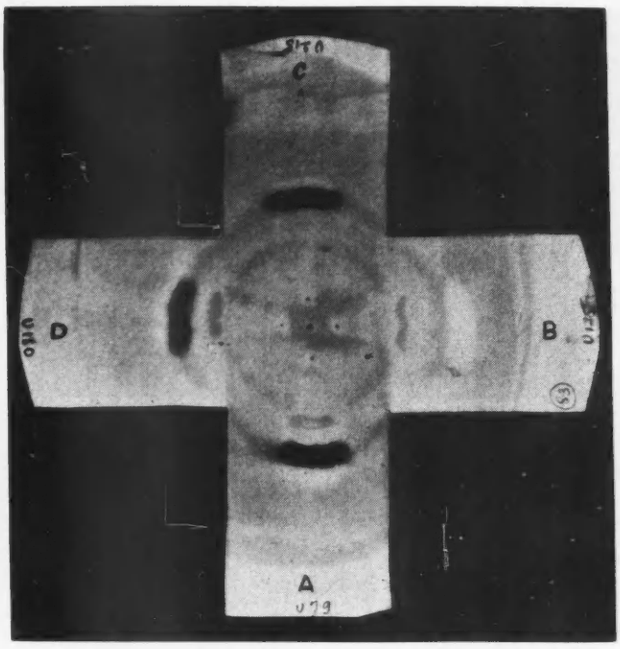

Fig. 2.—Screening test for mellituria, applying five microlitres of urine from each of four patients. Note the absence of sugar in Segment B and the presence of sugar in Segments A, C and D.

The wick is pushed half way through a hole in the centre of the paper, and the top of the wick is cut. The paper is mounted on the bottom half of a 15-cm. Petri dish containing 25 ml. of solvent, glacial acetic acid—ethanol—water (5:80:15v/v). In order to make the two parts of the Petri dish fit tightly and to provide a better seal, adhesive tape is wound around the rim of the lower half of the Petri dish. The dish is closed for approximately 45 minutes, the time it takes the solvent front to reach the edge of the dish. The chromatogram is then removed and the wick is discarded. After air-drying for a few minutes, the segment for the detection of mellituria is cut (Fig. 1) and stained with silver oxide as described. The remainder of the chromatogram may be stained with 0.25% ninhydrin in acetone for amino acids.[1] If the four segments are designed for the detection of mellituria, the whole chromatogram is stained with silver oxide (Fig. 2).

Staining

We find the silver oxide stain described by Trevelyn, Procter and Harrison[2] and Smith[3] most satisfactory because it leaves a pure white background and is highly sensitive. Because the staining solvents used are volatile and somewhat corrosive to the hands, it is suggested that the paper be manipulated with spring-type wooden clothespins.

The chromatogram is dipped for 10 to 15 seconds in a 1% solution of silver nitrate in methanol. After air-drying for less than one minute, it is dipped in 0.5% sodium hydroxide in methanol and is quickly withdrawn (30 seconds). The stained brown paper is drained of solvent by touching the dependent edge against the wall of the container, and is immediately immersed in a modified "hypo" photographic fix. Commercial "hypo" solution (for example, Kodak F-5) that has been diluted four-fold with 5% aqueous acetic acid is very suitable for this purpose. Alternatively, a litre of modified fix may be prepared by dissolving 12 g. of boric acid in 300 ml. of hot water, cooling, and adding 25 g. sodium sulfate, 25 g. potassium alum, and 50 ml. glacial acetic acid. This is mixed with a solution of 100 g. of sodium thiosulfate ("hypo") in 650 ml. of water. An immersion time of more than two minutes in the fix is not recommended, because of a slight tendency for the reduced silver to bleach. The fixed paper is then washed in a tray of water. Agitated water (i.e. running water) is not recommended, because the wet paper is fairly soft and tears easily. After 10 to 15 minutes' wash, the developed and stained paper is hung up to air-dry.

The normal urine, which shows no band, is scored zero. When sugars are present, a dark band appears and is scored from 1 to 4 according to the intensity and width of the band. The chromatogram can be stored in the deep freeze for preservation.

In staining large chromatograms (i.e. 18″ x 18″) a plastic screen may be used as a tray to carry the delicate paper from one solution to the next after the initial dip in silver nitrate. Such a chromatogram is dried by placing it on a flat absorptive surface.

Ascending unidirectional chromatography was used to study further the abnormal reducing substances detected by the screening test. In this procedure an 18″ x 18″ Whatman No. 1 paper is used and is marked off 1½″ from the bottom, by dots

TABLE I.

Patient No.	Age (years)	Diagnosis	Uristix test	Benedict's test	Screen test for sugar	Chromatographic identification	Urinary amino acids: A.N./24 hours in mg.	Urinary amino acids: A.N./T.N. × 100
1	4/12	Glycoaminoaciduria	4	4	4	Glucose	94.1	3.37
1a	8/12		4	3	4	Glucose	30.1	1.38
2	39	Father of child with cystinosis	4	2	4	Glucose	57.6	
3	48	Wilson's disease	4	2	4	Glucose, fructose	212.0	2.36
3a			4	1	2	Glucose, fructose	254.0	2.17
4	4	Acute leukemia	4	2	4	Glucose	35.4	1.57
5	31	Chronic renal disease	4	2	4	Glucose	256.0	
6	5-9/12	Aplastic anemia	4	1	4	Glucose	92.8	
7	4-3/12	Cystinosis	4	2	3	Glucose	59.5	
7a	5-4/12		4	2	3	Glucose	82.2	1.48
7b	6		2	1	1	Glucose, galactose	46.0	0.90
8	5-9/12	Pancreatic insufficiency	4	1	2	Glucose	41.9	0.56
9	1-1/12	Malnutrition	4	1	1	Glucose	25.4	1.00
10	1-1/12	Bilateral talipes equinovarus	4	1	1	Glucose	11.2	1.48
11	9-1/12	Acute leukemia	2	3	4	Glucose	200.0	1.57
12	12	Cystinosis	2	1	4	Glucose	753.0	6.60
12a	12		1	2	4	Glucose	535.0	5.60
13	25	Mother of child with glycoaminoaciduria	2	1	2	Glucose	99.4	1.14
14	14	Resistant rickets	2	1	1	Glucose + unknown	83.3	1.13
15	7	Cystinosis	2	0	1	Glucose	47.1	0.85
16	6/12	Myoclonic seizures	2	0	1	Glucose	73.0	0.93
17	6	Acute leukemia	1	1	4	Glucose + unknown	70.0	0.94
18	2-10/12	Celiac disease	1	±	1	Lactose	33.9	0.55
19	5	Multiple congenital anomalies	1	±	1	Lactose	10.9	2.46
20	5	Mental retardation	1	1	1	Glucose	6.0	0.73
21	47	Nephrosis	0	0	2	Lactose	61.5	1.17

spaced 1″ to 1½″ apart. A mixture of the standard sugar solutions is applied at both end spots, and the specimens to be examined are applied at the other spots in amounts of 25 microlitres. If a quantitative estimate is desired, standards of varying concentration are applied and the size and intensity of spots are compared. The solvent is 2-butanone–pyridine–water (5:3:2v/v) and is allowed to ascend to the top of the paper, which requires approximately 18 hours at room temperature. After air-drying, the silver oxide stain is used. In native urine a "white spot" due to the presence of urea may appear at the region of glucose and galactose and thus distort the typical round spots of these two sugars. This artefact is more pronounced when the concentration of urea is high or when the concentration of sugar is low. To prevent this distortion, the urea can be removed from the urine by urease digestion. To 4 ml. of native urine is added 0.5 ml. of a 0.5 M phosphate buffer, at pH 6, and 0.5 ml. of an extract of commercial urease (1 g. per 15 ml. water, centrifuged to clarity), and the mixture is allowed to digest at room temperature for two hours. Urea invariably disappears, but a new "white spot", this time due to ammonium chloride, appears on the chromatograms. Fortunately this is located in a non-critical region. Other non-carbohydrate reducing substances found in normal urine may yield a series of spots on the chromatogram, but the concentration of any one of these compounds rarely exceeds 10 mg. %. The position and intensity of these spots do not interfere with the identification of sugars found in urine.

Materials

Two hundred and forty-three specimens of urine previously studied in detail for amino acid content were examined for mellituria. In addition to the screening test with the silver stain, each specimen was tested with Benedict's reagent and Uristix. The specimens studied were obtained from 35 healthy children and 208 infants and children with a variety of conditions such as anemia, malnutrition, neurological, gastrointestinal and metabolic disorders and congenital anomalies. In addition two patients are selected to illustrate the diagnostic value and clinical application of the combined screening test.

RESULTS

Of the 243 specimens of urine studied, 217 gave negative results for sugar by the screening test, Benedict's test and the Uristix test. In the remaining 26 samples from 21 patients a positive Benedict or Uristix test was accompanied by a positive screen test, as shown in Table I. In five instances, the Benedict test was negative or questionable for cases in which the screen test was definitely positive. In two samples of urine from a patient with Wilson's disease, fructose was detected in addition to glucose. In one patient with celiac disease, lactose was found in the urine. Similar observations have been recorded by Bickel.[4]

Table I also lists the values for alpha amino nitrogen content of the 24-hour urine, and the index of the alpha amino nitrogen/total urinary nitrogen x 100. The alpha amino nitrogen excretion per 24

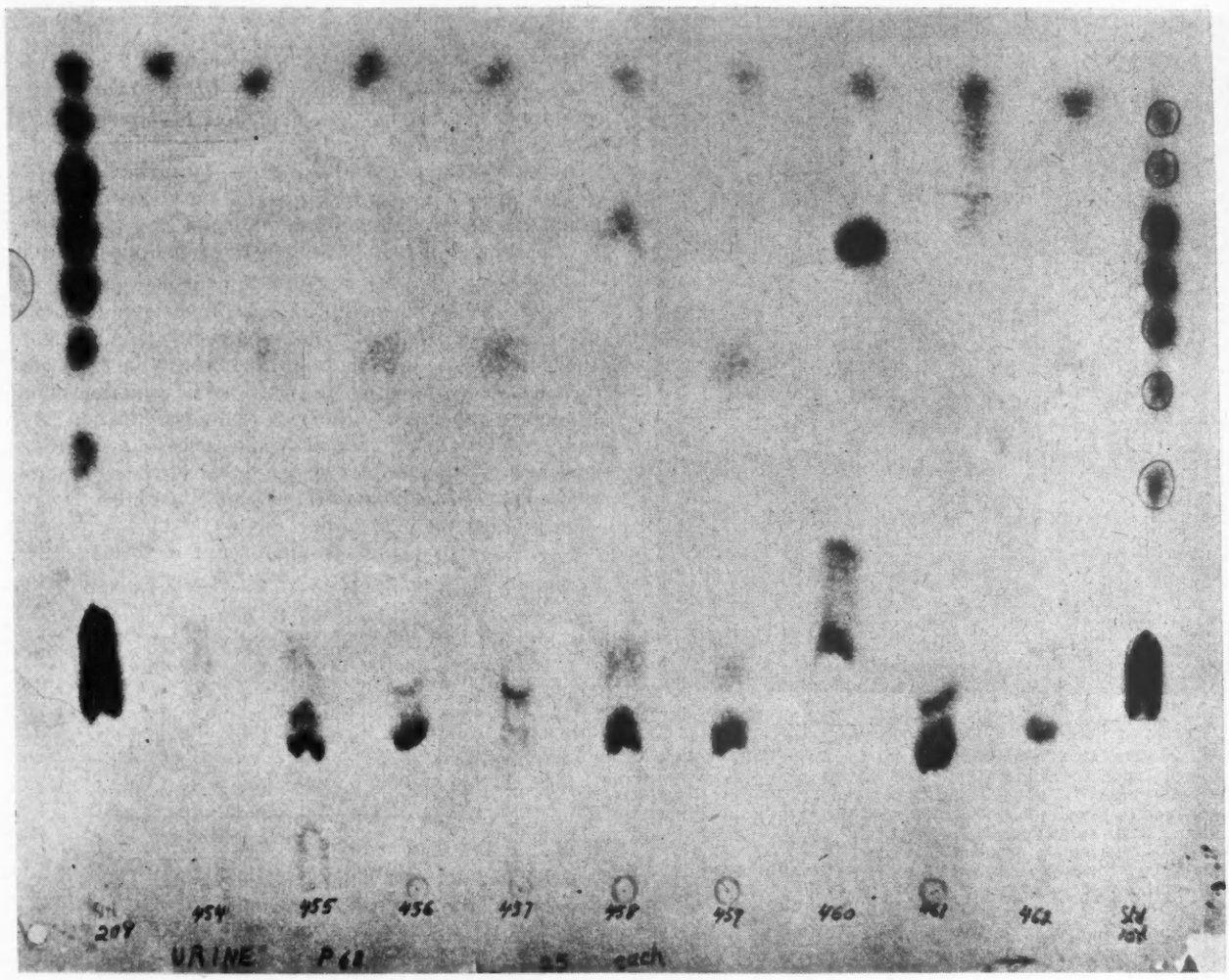

Fig. 3.—Unidirectional sugar chromatogram. Twenty-five microlitres of nine urine specimens applied at the spots indicated. The standard solution contains (ascending order of the spots) glucuronic acid, lactose, maltose, galactose, glucose, fructose, mannose, xylose and ribose. The concentration of each sugar in the mixture is the same. Five micrograms of ribose was applied to each urine spot to show the extent of migration. Note the glucose spot in the third urine from the right.

hours was found to be above normal in seven patients (Nos. 1, 3, 5, 6, 7, 11 and 12) and the index of alpha amino nitrogen/total urinary nitrogen x 100 was above 2 (the upper limit of normal) in six instances. The mean value of this index for controls is 0.8.[5] In 23 out of 26 specimens this index was exceeded. The association of mellituria with increased amino acid excretion is well documented.

Fig. 3 illustrates the unidirectional chromatogram of nine urine specimens with the two standard mixtures at each end.

Examples of the application of the combined screening test as a diagnostic aid are illustrated in two patients (Fig. 1 from Case 1 and Fig. 4 from Case 2).

CASE 1.—This infant male was first admitted to another hospital at the age of two months because of repeated episodes of melena, otitis media, fever, jerky movements and feeding difficulties. He was found to have an elevated NPN value (60 mg. %), pyuria, tachypnea, and high blood CO_2 and chloride values. He was treated for pyelonephritis and showed some improvement. Although the question of adenoma sebaceum was raised, the nature of his disease went unrecognized. The patient was referred to one of us (H.S.) for further study.

On admission he appeared well nourished, pale, hyperactive and fussy. He had a high-pitched cry and laboured respiration. He had numerous small raised punctate lesions over the forehead, with a butterfly distribution on the face. He appeared spastic with hyperactive deep reflexes. The costochondral junctions were prominent. Because of this latter finding, a urine sample was immediately examined by the combined screening test. The routine laboratory analysis of the blood and urine did not provide a clue as to the diagnosis. The positive findings of aminoaciduria and mellituria (Fig. 1) suggested an early diagnosis of cystinosis.

CASE 2.—The second patient, with a strong family history of galactosemia, had been fed Nutramigen® since the fifth day of life. He was admitted to hospital for study at five weeks. While on the Nutramigen diet he did not show any of the characteristic clinical features of galactosemia. A whole-milk formula was given in two successive feedings. Urine samples were obtained prior to and twelve hours after the initial

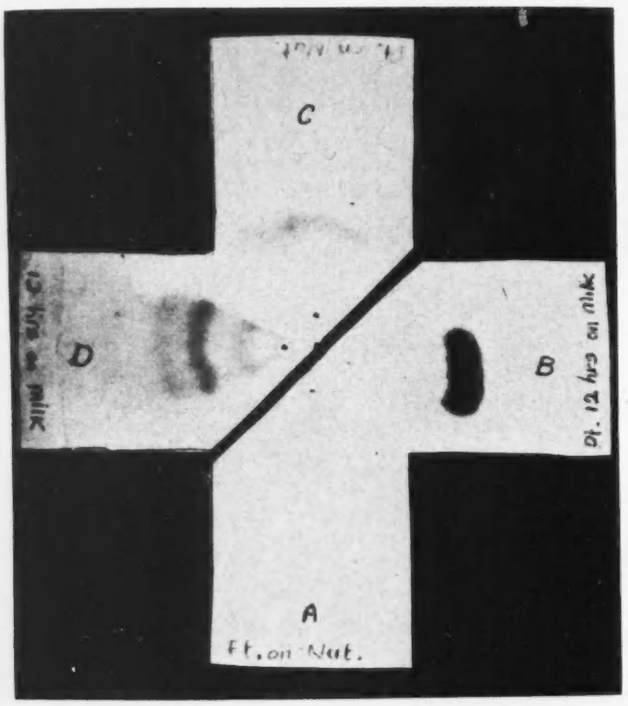

Fig. 4.—Combined screening test from Case 2. Five microlitres of urine used in each segment. Segments A and B stained for sugar; Segments C and D, for amino acids. Segments A and C while patients fed Nutramigen. Segments B and D, urine 12 hours after whole-milk feeding. Note the absence of sugar on Segment A and the very light stain for amino acids in Segment C. The heavy band in Segment B and the appearance of heavier bands for amino acids in Segment D is significant and suggests the diagnosis of galactosemia.

whole-milk feeding. The results of the combined screening test are shown in Fig. 4. Note the absence of sugar and the very low concentration of amino acid in Segments A and C in the initial specimen. After the milk feeding the urine showed mellituria and an increase in the amino acid excretion. The rapid appearance of mellituria following the lactose feeding, especially in association with increased excretion of amino acids, suggests the presence of galactosemia. The sugar was identified as galactose by the unidirectional chromatogram. The rapid increase in the amino acid excretion, though of diagnostic value, may not reach the defined or accepted level of aminoaciduria unless the injurious effect of galactose persists for one to two weeks.

Sucrose is not detected by the screen test or by Benedict's reagent because it is non-reducing. However, hydrolysis of the urine in 1N HCl for five minutes or digestion with sucrase will yield fructose and glucose which can be detected readily.

Benedict's test is non-specific, and its sensitivity is limited to approximately 200 mg. % of reducing substance (as glucose). By the chromatogram screening test using five microlitres of urine, as little as 1 microgram (20 mg. %) can be detected. The sensitivity can be further increased by applying increasing volumes (e.g. 25 microlitres will increase the sensitivity fivefold). However, by applying large volumes, compounds are concentrated which may interfere with the interpretation of the test.

SUMMARY

A rapid screening test for the detection of mellituria is described. This procedure can be performed in a combined fashion for the detection of aminoaciduria as well as mellituria. The frequent association of mellituria with aminoaciduria is documented. The sensitivity of the screening test for sugar is basically unlimited and depends on the volume of urine applied. Using five microlitres of urine, the sensitivity is approximately 20 mg. %.

The presence of mellituria was investigated in 243 specimens and the results have been presented. Sugars other than glucose, such as lactose, galactose and fructose, were detected. An improved unidimensional chromatographic technique for the identification and semiquantitation of reducing substances in urine is described. Two examples of the value of the combined screening test as a diagnostic aid are illustrated.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

SMALLPOX AND VACCINATION

Smallpox has been cropping out during the past year in so many places in Canada, and the laws in a number of the provinces are either so laxly enforced or rendered so ineffective with "conscience" and other restrictive clauses, that some consideration of the value of vaccination in preventing the spread of smallpox seems warranted. The public mind has been so wrought upon of late by anti-vaccination literature that it has come to look with suspicion, if not with hostility, upon this measure.

As is quite well known, previous to the discovery by Jenner, at the close of the eighteenth century, that an inoculation of cow-pox lymph afforded protection against attacks of smallpox, this disease was one of the scourges of Europe. The mathematician Bernouilli estimated that fifteen millions of persons died every twenty-five years from this cause, and de la Condamine affirmed that it destroyed, maimed, or disfigured one-fourth of mankind. Mercurialis, in the sixteenth century, took it for granted that everyone must have smallpox at least once in his life, and a German proverb, current in the eighteenth century, ran: "Von Pochen und Liebe bleiben nur wenige frei." If the mortality which prevailed in England during the latter half of the eighteenth century were the same today, it would represent an annual death rate of seventy thousand persons.

As is also well known, with the introduction of vaccination a profound change in this condition was effected, a change which has brought in England, where vaccination within recent years has not been universally compulsory, the average death rate of four per thousand in the eighteenth century down to 0.013 per thousand during the years 1891-1900, that has made it possible for the Prussian Army from 1874 to the present time to escape without a single death from this disease, and that has practically stamped out smallpox in Germany, a country where vaccination is compulsory from the second year of life. What is being accomplished today, however, is not so well known.—Editorial, *Canadian Medical Association Journal*, 1: 545, June 1911.

MEN AND BOOKS

EDINBURGH AND CANADIAN MEDICINE: THE FIRST ALEXANDER GIBSON MEMORIAL LECTURE*

PART II

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NOVA SCOTIA

NOVA SCOTIA early in the 19th century had about 60 physicians in the province, many of them with old-country degrees. In Nova Scotia the preponderance of Scottish-trained men again becomes evident. Of 14 practitioners in Halifax in 1845, 13 had studied in Edinburgh.

DR. JAMES SKINNER (Edinburgh 1800), who settled in Pictou, was probably the first Nova Scotian physician to hold a degree. Dr. Alexander MacDonald (Edinburgh 1805), who settled in Antigonish, was one of the founders of the Antigonish Highland Society. Early in the century ambitious young Nova Scotians turned their eyes towards Edinburgh, reputed to be the best Medical School in Europe, and there I quote from Dr. K. A. McKenzie's recent paper to the Nova Scotian Historical Society. The first Bluenoses to go to Edinburgh were W. B. ALMON and ROBERT BAYARD, both of whom received medical degrees and returned to their native province. Dr. Almon, who practised in Halifax, died of typhus fever at the age of 52. Dr. Bayard, after a few years of practice in Kentville, moved to Saint John where he and his son John were leading physicians for many years.

In the next forty years, 25 Nova Scotians trained at Edinburgh and returned to the province, bringing, it is said, and again I quote, the best medical knowledge of the period.

Training in the old country was expensive and few could afford to go. Crossing the Atlantic took three to six weeks in a sailing ship and students had to remain in Europe till their training was complete.

When we review the teaching of medicine in the maritime provinces, we see the hand of Scotland in the foundation of the Dalhousie Medical School. It was founded in a curious way. The customs duties collected at the Port of Castine were separately accounted for and formed the Customs Fund. The Governor, the Earl of Dalhousie, a Scot, proposed in 1817 that a considerable part of the fund should be appropriated to the founding of a college or academy on the same plan and principle as that in Edinburgh. Thus it came about that some £10,000 was used to found an academy which bears the proud name of its founder. It was not, however, till 1863 that steps were taken towards the establishment of a Medical Faculty. The Dean of the Medical Faculty was the aforementioned Almon.

Among the advocates of a Faculty and the use of the Victoria General Hospital was one whose zeal, energy and resourcefulness brought him later on to a position of great eminence in Canadian affairs—Dr. (afterwards Sir) CHARLES TUPPER. Dr. Tupper was born in Nova Scotia and took his M.D. in Edinburgh with a thesis on the management of parturition, illustrated by 116 cases, indicating a rather unusual range of experience in a youth of 22. There can be no doubt of his medical ability, but as Osler said of him, "He was a politician first and a practitioner only when stranded by the exigencies of party." He was the first President of the Canadian Medical Association and was exactly the right man to lead the Association in its formative years. He became Premier of the Dominion in 1896 and lived to the age of 94 in spite of being warned at the age of 59 that he had Bright's disease. Osler used his case in the paper—"The Advantages of a Trace of Albumen and a few Casts in the Urine of Men above 50 Years of Age".

Among the four original Vice-Presidents of the Association three held degrees from Scottish universities: Hector Peltier of Montreal and R. S. Black of Nova Scotia, from Edinburgh; and Botsford of New Brunswick, from Glasgow.

LOUIS SILVER—Edinburgh 1889—was a contemporary of Conan Doyle. He was Professor of Physiology in the old Halifax Medical College, and later Professor and Head of the Department of Medicine at Dalhousie. "Bunnie" Silver (hare lip) was a remarkable clinical teacher and diagnostician, in a quiet way almost equal to Bell himself as an observer of clinical data. The stories concerning him were legion. He was the son of an old Halifax mercantile family. His widow lives in Halifax, and his son, Dr. Gordon Silver, practises in Sherbrooke, N.S.

Within the present century the man of Edinburgh vintage who made the greatest impression in the Maritimes was JOHN CAMERON, Professor of Anatomy at Dalhousie, 1916-1930. He graduated from Edinburgh in 1904. He was the author of several books on anatomy and anthropology and an excellent teacher. He is retired and lives at Bournemouth, England.

One of the most outstanding of the medical men in the maritime provinces with an Edinburgh medical education was JOHN STEWART. His memory has

*Delivered at the University of Manitoba, Winnipeg, Man., January 17, 1961. This is the second of two instalments in which this lecture is being published.
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remained as an inspiration to those who knew him, and his tradition has lived in his native province and in the medical school to which he gave such exemplary service.

He graduated M.B., C.M. in Edinburgh in 1877 and it is good to know that after graduation he was invited by the great Lister to go to London when the latter was invited to accept the Chair of Clinical Surgery at King's College Hospital, London. In later years Stewart used to recall vividly how he rode to Lister's first lecture in a cab carrying with great care the culture tubes demonstrating the presence of living organisms. It was a day of days and one on which the sun rose to give new light and hope to a suffering world. For Lister's theories were not accepted there and he only went to convince them and spread his gospel farther afield, for he had supreme faith in its value—a faith amply justified by time. Lister's faith in his young house surgeon was also amply justified. Stewart, a man over six feet in height, handsome, dignified and of gentle bearing, could look forward to a career full of honours and achievement. But within a year, if such a dream existed, it had vanished, at least for the moment. His father had died and he was needed at home in Nova Scotia as the head of the family. If he had regrets nobody knew it. He returned and began to practise in Pictou.

When he began his practice there was but one general hospital in Nova Scotia—the Provincial and City Hospital in Halifax. That was 100 miles distant and so as a result, and in keeping with the practice of that day, surgery was done at home. Stewart had brought with him from London a Lister spray and, what is more important, all the knowledge of antiseptics. He had been brought up in the Edinburgh school where speed and dexterity had been highly valued and of these he made full use, but with them he exhibited a fine degree of care and thoroughness.

I have to thank Dr. Scammell for my information about Dr. Stewart, and no one could do it better, for Scammell actually gave the anesthetic on occasions for Stewart's operations. He described for me a case. Before the operation the surgeon gathered the family together in the kitchen and in a simple, unaffected way told them what he was going to attempt, and ended by asking for God's help in the task before him. He removed the head of the femur, lying in an abscess cavity, and closed the incision without drainage. The wound healed by first intention. Years later he was asked what had become of the patient. Said he, "You see that man ploughing over there? That is he." Forty years had passed.

As the prospects were so limited in Pictou, Dr. Stewart in 1894 moved to the capital city and was at once appointed to the Faculty of Medicine at Dalhousie. There he succeeded beyond the most sanguine hopes.

He was President of the C.M.A. in 1905 and in 1913 became Professor of Surgery at Dalhousie University. The great war saw him in command of No. 7 Stationary Hospital in France and there on his 70th birthday he met and conversed with King George V.

Following his return from the war he began to retire gracefully, and honours began to crowd upon him. Edinburgh gave him an Honorary Fellowship in Surgery, and from Edinburgh, Dalhousie and McGill he received the honorary degree of LL.D. He delivered the first Listerian Oration to the C.M.A. in 1924. It reveals his unexcelled mastery of the English language, and it is good to know that there is now a Dr. John Stewart Memorial Lecture each year at Dalhousie University.

I happened to be secretary of the Listerian Committee at the Centenary Celebrations of the B.M.A. in 1927 when I had the privilege of meeting Dr. Stewart.

KINGSTON, ONTARIO

In Kingston, Ontario, in 1855 it was resolved that a Medical Faculty be established within Queen's College, and of the six original professors we find that two of them held Edinburgh degrees. DR. JOHN STEWART was born in Perthshire and was an L.R.C.S. of Edinburgh. He came to Canada in the thirties of the last century and in 1839 was licensed to practise by the College of Upper Canada.

When he walked abroad in Kingston he sported the Kilmarnock bonnet and Stewart tartan plaid alike in summer and winter. This was symbolic of a self-assertive and combative temperament which brought much trouble to himself and to others whom he was fond of haling to the courts where he conducted his own cases and fought things out to the bitter end. He even fought a duel with one Steers, an equally hot-headed Celt from Ireland.

Stewart had studied anatomy under the brilliant Dr. Knox of Edinburgh and became the first Professor of Anatomy in this young Medical Faculty of Queen's.

Stewart was one of the picturesque citizens of Kingston. He is said to have made a good end at last under the discipline of age, infirmities, and, it is feared, straitened circumstances.

DR. FIFE FOWLER was born in Elgin, Scotland, in 1823. He was a pupil in the grammar school of Aberdeen, and after taking his M.B. there he proceeded to Edinburgh where he took his L.R.C.S. In the spring of 1854 he came to Quebec as surgeon of an immigrant ship and then pushed up country to Kingston where he settled and eventually was added to the staff of the Medical Faculty as Professor of Materia Medica.

Of the six professors in the original Faculty, two were Edinburgh men, two were from Ireland, one from Philadelphia and one from South Australia.

NEWFOUNDLAND

We read that the first colonists to reach Newfoundland in 1610 had no doctors with them. After

spending ten months in Newfoundland it was suggested to Guy, the leader of those early colonists, that he should have a doctor. His only comment was that only four had died during the winter and in his opinion all of them, if they had had as "good will to work as they had had good stomachs" for their victuals, would long since have recovered.

DR. WILLIAM CARSON, an Edinburgh graduate, has left a name for his fearlessness in urging reform of the government of the island and was chiefly instrumental in having the first hospital for civilians built in St. John's in 1813. Before that two military hospitals existed, one for infectious diseases, but they were largely for the soldiers of the garrison.

NORTH WEST TERRITORIES

In the North West Territories, which comprised what is now Alberta and Saskatchewan, there were occasional medical men with explorers and fur-trading settlements. DR. JOHN RICHARDSON, who was with Sir John Franklin on his overland journey to the Polar Sea, makes reference to Edmonton in 1820, it having been founded in 1795 as a fur-trading station, as having much goitre.

Richardson was a medical man whose name was closely associated with the North West Provinces of Canada and the Arctic region. He was a graduate of the Edinburgh School of Medicine (1807, later F.R.C.S.E.), and a naval surgeon who accompanied John Franklin on his first two Arctic expeditions. He became the leading authority of his day on the Arctic regions and subsequently led one of the Franklin rescue expeditions.

It is likely that Franklin's first expedition would have ended in disaster and the death of all its members had it not been for the courage, resourcefulness and great physical strength of this brave and steadfast man. In addition to being surgeon to the two expeditions, Richardson was botanist, icthyologist and biologist.

The first expedition in 1819, after passing the winter on the Saskatchewan river, succeeded in reaching Fort Providence in 1821, and got back only after the most terrible experiences. In the second expedition he accompanied Franklin to the mouth of the Mackenzie River in 1825 but got separated from the party in 1826 and explored the coast to Coppermine River and the Great Slave Lake. Undaunted, he conducted a search exploration for Franklin in 1847. In spite of an early start Richardson did not progress as far as he had hoped. Impassable ice barriers compelled them to abandon their boats and cut across the Barren Lands. They spent the winter at Fort Confidence and returned to England in November 1849.

It was fourteen years before the fate of the Franklin expedition was solved, when McLintock discovered the cairn which contained a brief account of their expedition. Abandoned boats and bodies were also found.

JAMES WHITE, M.D., who studied medicine at the University of Edinburgh, and was for a time an assistant apothecary in the city, and later, from 1809 to 1811, assistant surgeon in *H.M.S. Beagle*, came to Red River in 1814 as surgeon to the colony. He was appointed at a salary of £50 per annum, lodging and subsistence for the first two years, and 500 acres of land.

An interesting Edinburgh surgeon who did something for Canada, in this case also in the field of exploration, was SIR JOHN RAE. He was born in Orkney and educated in Edinburgh, taking his M.B. and F.R.C.S.(Ed.) in 1833. He joined the Hudson's Bay Co. as a surgeon—a somewhat unusual appointment since no other surgeon is recorded in the Company. He became an able and successful explorer, in large part because of his courage and resourcefulness and because he lived off the country as did the Esquimaux and Indians, so avoiding the necessity for cumbersome expeditions carrying supplies. He did important geographical work in the north of Canada and in 1847 joined Sir John Richardson's expedition in search of Franklin. In charge of a later expedition in 1853 he was successful in discovering the fate of Sir John Franklin's expedition. He found none of the bodies but he did collect from the Esquimaux unmistakable evidence of their fate in the form of personal equipment such as watches and a medal—Sir John Franklin's Order of Merit. This was the first evidence of the fate of the expedition.

WINNIPEG

As we proceed west in the story and come back to our starting point, we find that the cycle of time changes. For while on the seaboard the time of early medicine was a matter of centuries ago, here in Manitoba early medicine is much later. That is not surprising, for Winnipeg a little over a hundred years ago was a "straggling little hamlet" and, indeed, it was not till the completion of the Canadian Pacific Railway in 1885 that the western part of Canada gained direct communication with the East. So we find that there, some of the pioneers of medicine were alive in our lifetime.

But although Winnipeg was then still a pioneer town with its main connections to the outside world by river steamer to the south, in 1877 the University of Manitoba was incorporated. The University, the oldest in the Canadian West, was instituted by the union of Roman Catholic, Anglican and Presbyterian Colleges and some six years later the legislature was requested to grant a charter incorporating the Manitoba Medical College. The physicians who were named as the incorporation were not fully convinced of the necessity for a new medical school but their hands were forced by a group of medical students whose importunity prevailed and the school opened.

Amongst the members of the first Faculty was ROBERT JOHNSTONE BLANCHARD—Professor of Anatomy, a native of Pictou, who graduated in medicine from Edinburgh. He was one of Lister's dressers there and came to Winnipeg in 1881, becoming

the leading surgeon, and in 1909 was President of the Canadian Medical Association. In 1915 he went overseas in command of No. 3 Casualty Clearing Station.

Up to 1910 the members of the Faculty had given their services without remuneration but in that year the first full-time appointment was made. This was to the Chair of Anatomy and was held for four years by Dr. Evat. His successors have been Alexander Gibson, J. C. B. Grant, and R. G. Inkster, all graduates of Edinburgh, so that that city seems to have had almost a monopoly of this Chair.

The post of Dean of the Faculty was held in 1912 by Dr. S. Willis Prowse, a native of Prince Edward Island and a graduate in medicine from Edinburgh. At the time of his appointment he was in command of a Casualty Clearing Station raised by the College. Under his direction the School made considerable advance.

The School from its inception has been modelled on the lines of the British Schools, and here I quote—particularly Edinburgh. It is interesting to read that in his inaugural address the Dean gave this advice to students, "Beyond all things, as you hope to master scientific medicine and practise it successfully, afterwards, do not make short work of your anatomy and physiology."

IAN MCLAREN THOMPSON went from Edinburgh to McGill as demonstrator in Anatomy about 1925 and later to California where he worked with Hervert Evans, the great worker on the pituitary gland. He came to Winnipeg about 1936 as Professor of Anatomy in the University of Manitoba.

SWALE VINCENT worked in Edinburgh with Sharpey Shaefer, who elucidated the effects of the pituitary gland on the blood pressure. From there he went to Winnipeg where he was Professor of Physiology.

On the medical staff of the University we have seen in recent years quite a few Edinburgh men—Inkster in Anatomy; Hay and Abbot in Clinical Surgery; Adamson as Associate Professor of Medicine; Davidson in Medicine; MacCharles and Sevrin in Clinical Surgery (F.R.C.S.(Ed.) 1924; Professor and Surgeon-in-Chief, W.G.H.); White in Biochemistry; McElmoyle in Anatomy—and, I have little doubt, others; certainly three others whom I would talk of now.

In 1908 three young men graduated in Edinburgh —one of them Alexander Gibson, whose memory we are honouring tonight. After a period of internship at the Royal Infirmary of Edinburgh, followed by a term in the Department of Anatomy, Gibson went to the Dreadnought Hospital, Greenwich, where he engaged in surgical work under the well-known Choyce. In the course of time Choyce received a letter from H. H. Chown, Dean of the Faculty of Medicine at the University of Manitoba, asking for suggestions as to a man who would make a good Professor of Anatomy in Winnipeg. Choyce had no difficulty in recommending Gibson for this position. As might well be imagined, he was an immediate and brilliant success in his new position because he was a born teacher and investigator.

Then came the war and at the end of 1915 Gibson obtained leave from the Department of Anatomy and joined the Army as a surgeon. On returning to Winnipeg at the end of the war Gibson decided to continue work as a surgeon rather than as an anatomist. The Dean of the Faculty asked him to suggest a successor in the Chair of Anatomy and Gibson had no hesitation in recommending J. C. BOILEAU GRANT, the second of the trio just mentioned.

Grant, after graduation and internship, spent two years with Professor Arthur Robinson in anatomy at Edinburgh and another two years with Professor Howden, at that time editor of "Gray's Anatomy" at the University of Durham. At the outbreak of war Grant joined the Army as a regimental medical officer and was with the Grenadier Guards and the Black Watch in that capacity. During this period he was awarded the Military Cross and later a bar to it. Coming to Winnipeg in 1919, Grant followed Gibson's footsteps and at once proved himself a superb teacher.

In 1920 he made an expedition into the north country in order to collect anthropological data regarding the Indians. This he did on six different occasions, penetrating as far as Hudson's Bay and what were then the North-West Territories. On these expeditions he earned from his Indian companions the name of "Strong Man" owing to the apparent ease with which he played his part in portaging even the heaviest canoes.

In 1930 Grant received an invitation to join the University of Toronto as head of the Department of Anatomy. Here he became one of the most outstanding teachers in the entire medical faculty, and wrote three books which carried his name throughout the world: "Method of Anatomy", "Atlas of Anatomy" and "Handbook for Dissectors".

The last of the trio who graduated in 1908 was WILLIAM BOYD. Boyd was Gibson's closest friend during their undergraduate years. On one occasion they bicycled in the English Lake District and spent two weeks hill walking. On the evening of the day when the final examination results came out, Gibson and Boyd, in company with four non-medical friends, took the night train to Oban, and next morning sailed over the sea to Skye, where they spent two weeks rock climbing in the Coolins.

Boyd intended to go into general practice, but after a year of internship he was offered the position of assistant medical officer at the Derby Borough Asylum. He spent the next three years in psychiatry, and obtained the graduate degree of Diploma of Psychiatry of the University of Edinburgh in the first year it was granted. He managed to pick up some knowledge of pathology in the course of his work in mental hospitals, and became the first pathologist to the Wolverhampton General

Hospital in 1913. In the summer of 1914, he received a letter from Gibson in Winnipeg asking him whether he would like to become Professor of Pathology at the University of Manitoba, although he had never published a scientific paper or taught one student. Boyd thought it would be fun, but when his appointment was confirmed in August 1914, he was already in a Field Ambulance of the 46th Division of the Territorial Army, with France as their destination. Later the University of Manitoba requested that Boyd be granted leave of absence from the Army to take up his teaching duties in Winnipeg, where young medical graduates for the armed forces were urgently required.

By the time Grant arrived in Winnipeg to succeed Gibson in the chair of anatomy, Boyd, a son of the manse, had married Enid Christie, a daughter of the manse. On the day Grant arrived Boyd invited him to his house for the evening, and also invited Catriona Christie, Boyd's sister-in-law. It was not long before these two were also married. None of these happy events would have been possible had it not been for Gibson.

Boyd was one of the great teachers of pathology. This is his greatest attribute and for it he will always be remembered. He has developed the teaching of pathology to a fine art. He has accomplished this first by his textbooks ("Textbook of Pathology", "Pathology for the Surgeon", "Pathology for the Physician" and "Introduction to Medical Science"); secondly by the development of a new principle in the arrangement of material in pathological museums; and thirdly, and much more important, by the quality of his lectures and demonstrations and the manner of his presentation of them. He condenses the pith of the problem he is presenting into as few words as possible, which can be presented without any appearance of haste; deliberately, almost slowly. A distinct lisp adds to the interest of his speaking. He is meticulous in his choice of the right word or phrase to make his meaning clear, and uses these in a manner so natural that there is no sense of stiffness or artificiality. Perhaps his splendid lecture teaching is derived from his Edinburgh training.

In 1937 the Boyds followed the Grants to Toronto. In 1957 Boyd and Grant returned to Winnipeg to take part in the 50th anniversary celebrations of the Manitoba Medical College. On that occasion Grant was awarded the honorary degree of D.Sc., and Boyd addressed the Annual Dinner. The only note of sadness was the absence of Gibson, who by that time had passed away.

And so I come to the end of a long story, but, I'm afraid, an incomplete one, and if the title appears to suggest somewhat vainglorious claims, it has confirmed that Edinburgh has left its mark on the medicine of Canada, even on the basis of numbers, and if, perchance, it has given something to Canada it has been amply repaid.

Whenever any one of the Edinburgh school, especially in surgery, seeks up-to-date information and methods, he crosses the Atlantic and, speaking for myself and many others, Canada is always our Mecca and we are never disappointed.

In this connection it is interesting to read in MacDermot's "Notes on Canadian Medical History" that, after remarking that up to 1914 those seeking postgraduate learning turned almost wholly to British and Continental centres, he says that the great expansion in hospitals and research centres in Canada has reversed the direction of postgraduate migration—and how right he is.

And so, if I have appeared to praise Edinburgh, I praise Canada at the same time, for it must be obvious that these men have loved Canada, their new country, better than their own.

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CASE REPORT

TREATMENT OF METASTATIC CARCINOMA OF THE THYROID WITH RADIOACTIVE IODINE*

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Edmonton, Alta.

THE STORAGE of I^{131} in a metastasis from a thyroid carcinoma was reported by Keston *et al.* in 1942,[5] and aroused considerable interest. First reports of clinical cases were disappointing, since only a few of all patients investigated apparently accumulated any I^{131} or sufficient amounts to lead to ablation. In the past 10 years, however, with the development of the scintillation scanner to visualize and locate the active areas and the introduction of techniques, such as the use of thyroid-stimulating hormone, to induce or increase the uptake of I^{131} of the tumour tissue, a new surge of interest has been shown in the subject and many excellent articles have been published.[1-4, 6-9]

It is considered essential to remove or ablate the complete thyroid gland before the metastases will become active and pick up iodine. Generally speaking, tumours showing the formation of follicles and which contain colloid are most likely to be responsive to I^{131} therapy; anaplastic tumours are least likely to be suitable. The pure papillary tumour and the majority of Hürthle cell types of malignant adenoma can only seldom be stimulated to concentrate I^{131}. Many authors point to the fact that the pathology is seldom of one type and perhaps the biopsy specimen in some cases is not representative. It is interesting to note that Blahd, Nordyke and Bauer[2] in a recent article consider that 80% of patients with thyroid cancers, that is to say the percentage showing differentiated tumours, are potential candidates for I^{131}. They further find that four out of five benefit to some degree although not all of these are by any means cured.

Before the general introduction of scintillation scanning as a routine procedure in larger isotope centres, the amount of I^{131} from a tracer drink not excreted in the urine over the first 24 to 48 hours after the drink, was used as an indication of the likelihood that a patient would be a suitable candidate for I^{131} therapy. Localized areas on scans are used more routinely today, and provided that all subsequent scans are carried out under identical conditions with regard to dose, time factor, scan speed and the length of time the patient is off thyroid medication before an assessment, then the scans form a useful visual aid in judging the progress of ablation of metastases.

Turnover rate of the iodine in the tumour is important in the outcome of therapy. If the iodine is excreted too rapidly from the cells, it is difficult to irradiate the tumour to a sufficient degree. Uneven distribution of the iodine within a tumour also makes it difficult to destroy with a single dose. Repeated doses over an extended period with repeated assessment between treatments is necessary. The following case illustrates the interesting and highly satisfactory results of such extended treatment.

Mrs. A.F., aged 57 years, was first admitted to the University of Alberta Hospital on February 3, 1955. Her chief complaint was that she choked on attempting to swallow food; episodes of this complaint had become worse during the previous six weeks. Her voice had been changing over the past year and she also complained of chronic cough. In 1947 the patient had had a partial thyroidectomy. At that time the pathological features of the gland were reported as follows:

The cut surface of the thyroid gland revealed nodules varying in size from 0.5 to 3.0 cm. in diameter with diffuse hemorrhagic areas. Sections showed densely packed adenomatous formation. The diagnosis was papillary carcinoma of the thyroid.

Physical examination in 1955 showed the left lobe of the patient's thyroid to be hard. A large mass filled the left pyriform sinus and caused external pressure on the larynx. The tumour was attached anteriorly and was freely movable. It displaced and compressed the trachea and esophagus to the right. Biopsy examination was negative.

A radioactive iodine test on February 10, 1955, showed the thyroid uptake to be 12.4% at 24 hours. The right side of the neck was more active than the left and there was some activity behind the midsternum. Despite the negative biopsy result this was considered to be an extension of the original carcinoma.

From February 15 to 28, direct cobalt radiation to a left lateral port of 12 x 10 cm. was given. The skin-to-source distance (SSD) was 80 cm.; skin dosage was 3250 r. A total dose of 4750 r was planned but discontinued owing to the condition of the patient.

From March 21 to April 5, parallel opposing fields were used anteriorly and posteriorly to the left side of the neck for radiation therapy (cobalt). The port size was 10 x 8 cm.; SSD, 80 cm.; and 1810 r incident to each field was given. The midline dose was 2500 r.

The patient was re-admitted to hospital on May 23, 1955, complaining of increasing low back pain. This was aggravated by coughing and sneezing. Sharp, shooting pains down the back of the left buttock and into the left thigh had progressed until the patient experienced difficulty in walking and sitting.

On May 26, thyroid uptake was 15.8% at 24 hours. Conversion ratio (protein bound iodine) (C.R.) was 14.0%. A search of the spine and chest showed no increased uptake. The chest radiograph was negative. A myelo-

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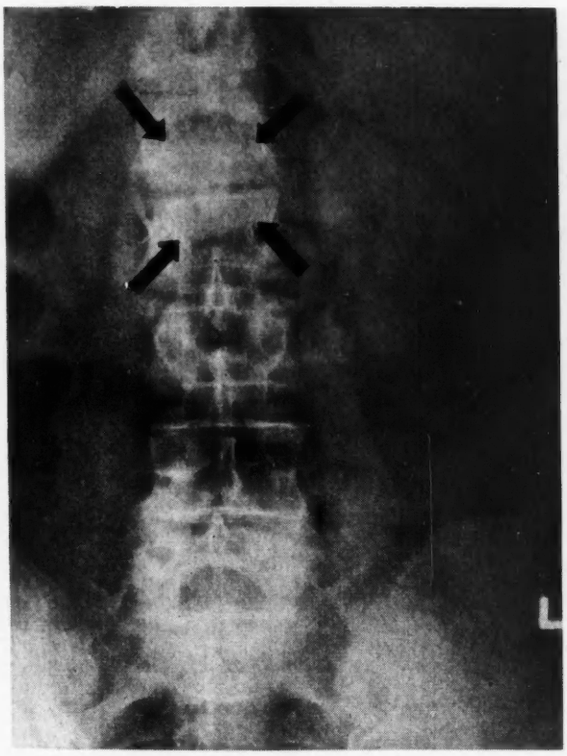

Fig. 1.—Radiograph of lumbar spine showing large osteolytic area involving L1 and L2, with destruction of the pedicles of L1 (May 17, 1955).

gram showed a block at the level L1-L2. A radiograph of the lumbar spine showed osteolytic areas involving L1 and L2 (Fig. 1).

May 31: 2800 r was given to the lumbar spine in seven treatments over nine days. Direct cobalt radiation was given to a 15 x 8 cm. port; SSD was 80 cm. The patient was much improved one month later, and continued so for about one year, at which time the pain in her back again became worse and she was confined to bed.

Fig. 2.—Lumbar spine, showing recalcification of the large osteolytic region involving L1 and L2 (February 11, 1957).

Fig. 3.—Radiograph of dorsal spine showing collapse of D5 (February 11, 1957).

Further therapy was given from July 25 to 27, 1956. A posteroanterior port, 10 x 20 cm., was used to the lumbosacral area, with an SSD of 80 cm.; 900 r was administered. The patient refused further treatment. Radiographs at this time showed again the destruction of L1 and L2.

The patient was again admitted on October 1, 1956, complaining of pain in the dorsal spine. This had begun six weeks before and became worse. She had been confined to bed since August. Cobalt therapy was given from October 1 to 15, 1956: to the lumbar spine, port 10 x 20 cm., 2750 r in 10 treatments; to the dorsal spine, port 15 x 10 cm., 2750 r also in 10 treatments with an SSD of 80 cm. The patient gradually showed improvement from the treatment.

Radiographs of the lumbar spine (Fig. 2) on February 11, 1957, showed some recalcification of the large osteolytic area involving L1 and L2. Films of the dorsal spine (Fig. 3) showed some collapse of D5. In May of 1957 the general condition of the patient had improved, although there was still some pain in the dorsal and lumbar areas. Indirect examination of the laryngeal area showed a clear unobstructed airway with some atrophy as a result of the previous radiation.

On May 11, 1957, the thyroid uptake was 17.5% at 24 hours. Increased activity was present over L1, L2 and the body of C7.

On May 29, 138 mc. I^{131} was given orally. The patient claimed to be improved at time of discharge one week later.

August 6: The radioactive uptake of the neck at 24 hours was 6.8%. L1, L2 and L4 showed uptakes of 15, 20 and 31% respectively. The uptake over the lower right chest was 14%. It would appear that the

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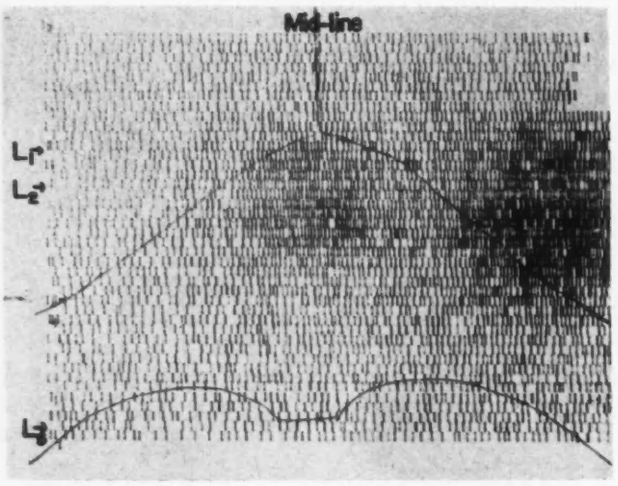

Fig. 4.—Scan showing marked uptake of I^{131} over L1, L2 and lower right chest (November 26, 1958). Scan performed 24 hours after administration of 100 μc. I^{131} (selector ×10, patient prone).

active areas of the neck had been partially ablated but that the metastatic areas of the spine were now rather active.

Mrs. A.F. continued fairly well until November 1958, being maintained on thyroid of which she could not have been taking more than ½ grain daily, even though more had been prescribed. Examination showed the pulse to be 90 and her skin warm. There was no exophthalmos, but lid lag was present. The patient reported considerable benefit from the iodine therapy but it was felt that functioning thyroid tissue was still present. The chest radiograph showed no evidence of metastases. Radiographs of the spine revealed the collapse of D5 to be almost complete but the lumbar spine remained the same. In view of the previous radiation to the spine it was decided that no further external radiation should be given.

On November 25, 1958, 100 μc. of I^{131} was given as tracer. The thyroid uptake was very small. Considerable uptake was present over the lumbar spine and lower right chest (Fig. 4).

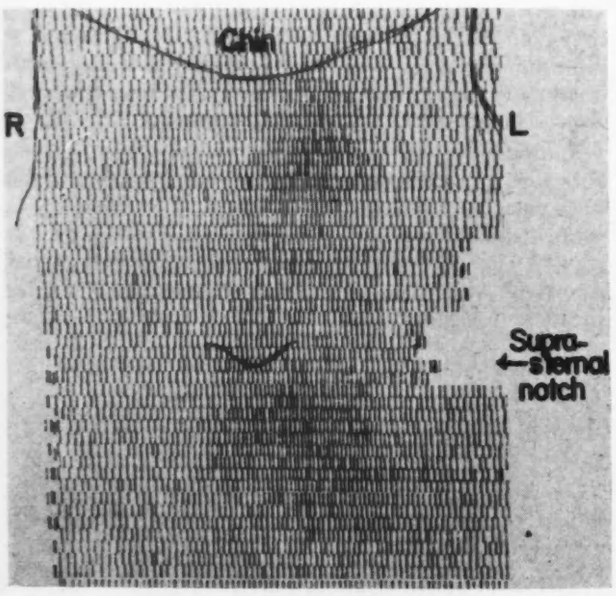

Fig. 5.—Scan of neck (January 6, 1959) three weeks after ablation dose of 100 mc. I^{131} showing activity in tumour in the neck to the left of midline and D5 (selector 40, scan-speed 10, patient supine).

In view of the high uptakes by the metastatic areas, 100 mc. I^{131} was given. Five days later the patient had what appeared to be a stroke. She was barely articulate and complained of pain in the left side of the head. There was paresis of the left side of the face and weakness of the right arm and leg. Reflexes were sluggish on both sides. It was thought that these findings were due to a cerebral extension of the metastatic disease. The patient made a dramatic and fairly prompt recovery during the weeks that followed and was discharged on February 4, 1959, walking without assistance and showing little residual evidence of the severe disability which had occurred in December.

During this period of hospitalization, urine and stool were collected and assayed for 13 days after the therapeutic I^{131} was administered. The radioactivity in the whole blood and the thyroid gland area were also measured over the same period. It was calculated that maximum thyroid uptake was 6% at 12 hours and 4.5% at 24 hours. The estimated dose to the remnant gland was 40,000 rad beta and 2795 for gamma radiation. The total radiation to the blood was 105 rad; total body, 114 rad; ovaries, 117 rad. The estimated uptake by metastatic areas was 30% of the total I^{131} administered. Fig. 5 shows the residual activity present in the neck three weeks after treatment.

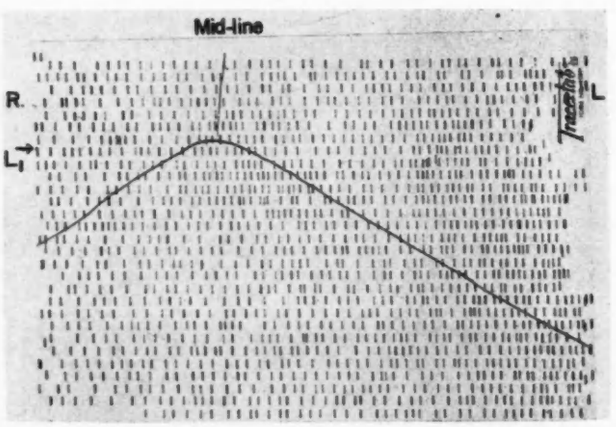

Fig. 6.—Six weeks after 100 mc. I^{131} (January 28, 1959). Only slight residual activity present. Patient scanned under same conditions as before.

On January 27, 1959, the thyroid uptake was 4.5%. The scintiscan is shown in Fig. 6. It was considered that the metastatic lesions had been ablated.

On March 29, 1959, the patient was again admitted to the University Hospital for reassessment. She had gained 12 lb. Her appetite was good. She was complaining of pain in the right side of her head. Skull radiographs (Fig. 7) showed osteolytic lesions, the largest of which was 1 cm. in diameter. The chest was clear and the lumbar spine showed marked recalcification.

On April 4, 1959, her thyroid uptake was 4.8%. Scans showed only slight activity over D4, D5, L1 and L2.

One hundred mc. I^{131} was given to attempt a final ablation of residual activity. Urine, stool and blood studies were carried out for nine days. Radiation to the blood was 29.6 rad; total body, 70.7 rad; ovaries, 73.1 rad. The patient's blood picture remained essentially normal and she was discharged well on April 17, 1959.

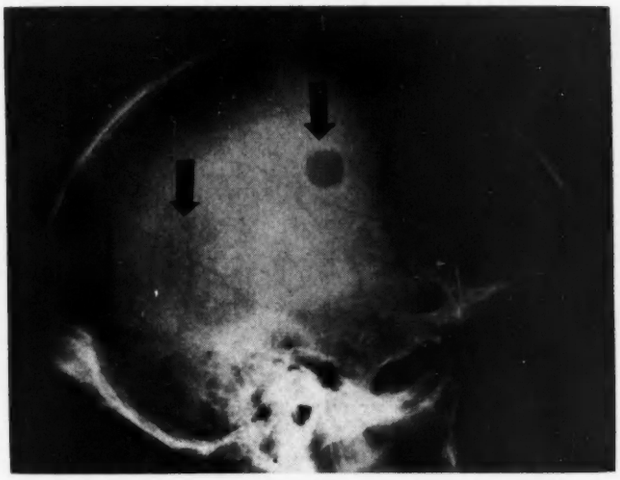

Fig. 7.—Skull radiograph showing round osteolytic areas in left parietal bone; the largest measures 1 cm. in diameter (March 31, 1959).

When the patient was next seen, on June 9, 1959, the most striking feature about her was the gross myxedema. She was started on 15 mg. thyroid daily, to be increased by increments of 15 mg. each week.

On June 10, 1959, only very slight radioactivity was found over D4, D5, L1 and L2.

August 12, 1959: Scans of L1 and L2 were negative. Fig. 8 shows activity over the dorsal spine. The patient continued to improve and was walking without a cane. She was taking 96 mg. thyroid daily but there was still some evidence of hypothyroidism and she complained of some pain in the head and lower back.

From October 6 to 27, 1959, a 20 x 7 cm. port was used for cobalt therapy centring over D5; 2000 rad was given in 10 treatments. A nodule in the right temple was treated using 140 KVP, 0.25 mm. Cu., 1 mm. Al., a port of 4 cm. in diameter, and an SSD of 23; 2500 rad was given in five treatments. Skin lesions were present over the ankles and these were treated as follows: to a circular area (2.5 cm. diameter) on the medial aspect of the right ankle 1400 rad was given; to an eliptical area (4 x 3 cm.) on the anterior aspect of the right ankle, 1000 rad; to a circular area (2.5 cm. diameter) of the sacroiliac region, 1000 rad. Other factors were as described above.

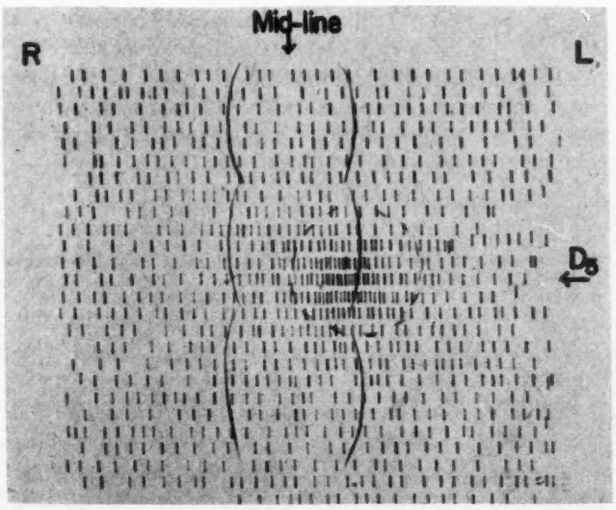

Fig. 8.—Scan showing uptake in the region of D5 (August 13, 1959). Patient prone, scanned 24 hours after administration of 100 μc. I^{131} (speed 10, selector 10, thyroid discontinued two weeks previously).

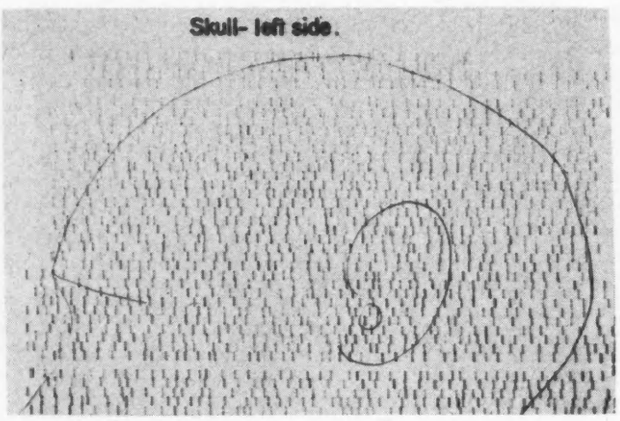

Fig. 9.—Scan of left side of head 24 hours after administration of 100 μc. I^{131} (selector 10, speed 10, patient off thyroid, discontinued two weeks previously). No observable uptake of I^{131} by osteolytic areas in left parietal or occipital bones (February 18, 1960).

On October 22, 1959, 500 μc. I^{131} was given but no increased uptake could be demonstrated over any of the nodules.

On December 8, 1959, the patient had no complaints, the nodules had disappeared and the scintiscan of skull (Fig. 9) showed no evidence of increased uptake. A careful total body search revealed only slight activity at D5.

On March 14, 1960, the patient was admitted for reassessment. Stimulation with TSH was attempted. The thyroid uptake was 7.3%, C.R. 53.1%. There was some stimulation of activity over D5 but the scan of the lumbar area showed no increase. The osteolytic areas in the skull had decreased slightly since previous x-ray examination (see Fig. 10). There was marked recalcification of L1 and L2 (Fig. 11).

On March 23, 1960, 60 mc. of I^{131} was given orally to attempt ablation of those areas still functioning. The urine, stool and blood activity was tested for 12 days with the following results: radiation to the blood, 27.9 rad; total body, 19.9 rad; ovaries, 32.7 rad.

On August 22, 1960, thyroid uptake was 1.4%, C.R. 9.3%; result of thyroid scan was negative (Fig. 12),

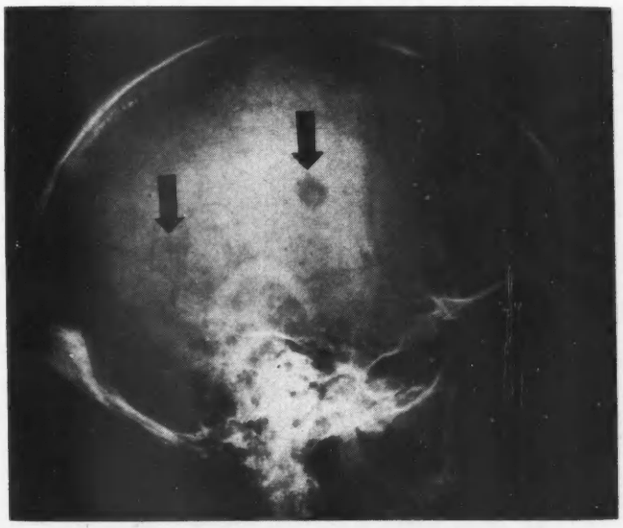

Fig. 10.—Skull radiograph showing the decreased size of osteolytic areas in left parietal and occipital bones (March 15, 1960).

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Fig. 11.—Marked recalcification of L1 and L2, particularly the pedicles and spinous process of L1 (March 15, 1960).

but D5 was still slightly active (Fig. 13). Radiographs showed complete collapse of D5. The scans of L1 and L2 showed slight activity (Fig. 14).

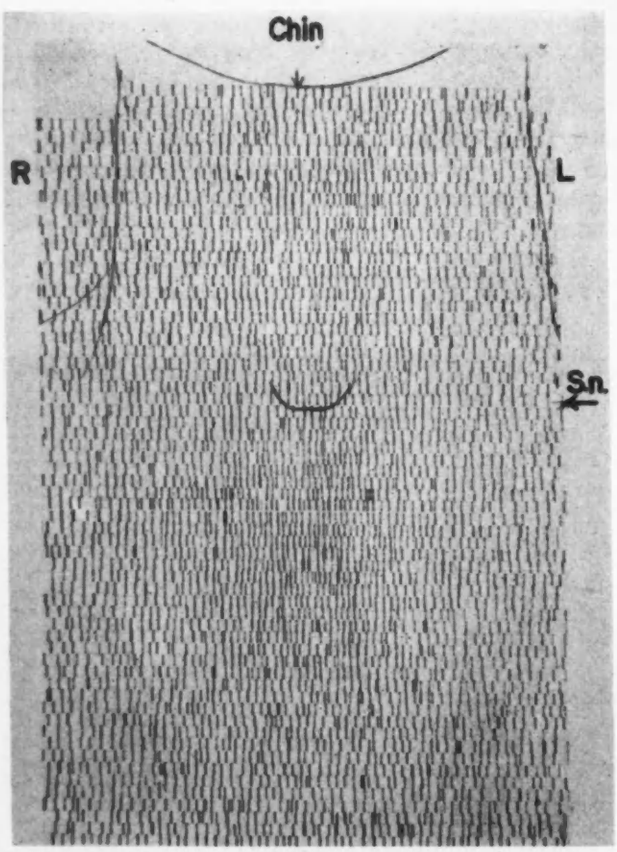

Fig. 12.—Scan showing marked decrease in activity in neck region (August 23, 1960). Taken 24 hours after administration of 1 mc. I^{131} (selector 20, speed 10, patient supine, thyroid discontinued two weeks previously).

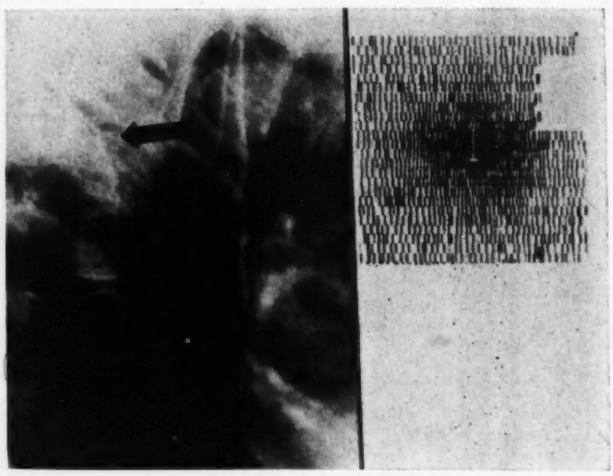

Fig. 13. — Radiograph shows complete collapse of D5 (August 22, 1960). Scan shows localized uptake of I^{131} at D5, 24 hours after administration of 1 mc. I^{131} (selector 20, speed 10, patient prone, thyroid discontinued two weeks previously).

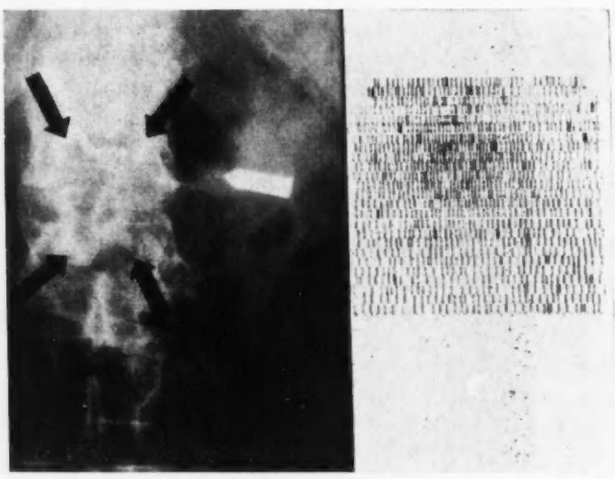

Fig. 14.—Radiograph shows little change in L1 and L2 from previous films (August 22, 1960). Scan shows localized uptake of I^{131} at L1. Taken 24 hours after administration of 1 mc. I^{131} (selector 20, speed 10, patient prone, thyroid discontinued two weeks previously).

The patient continues to be in relatively very good health and will return for reassessment and further treatment as required.

SUMMARY

A case of thyroid carcinoma in a 57-year-old woman who had skeletal metastases for six years has been reported, in which radioactive iodine and scanning techniques played an important role.

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SHORT COMMUNICATION

USE OF INTRACATH IN SPONTANEOUS PNEUMOTHORAX

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SPONTANEOUS pneumothorax is usually a benign condition of minimal extent and severity. It requires no specific form of therapy. After the patient has had a week or two of rest, the tear in the lung has usually healed and most of the air in the pleural space has been absorbed. Under certain circumstances, however, it is necessary to institute active treatment. The immediate treatment then consists in removal of the air from the pleural space.

The indications for removal of the air are: (1) tension pneumothorax; (2) a pneumothorax in which approximately 60% or more of the lung on that side is collapsed; and (3) a pneumothorax which does not respond adequately to conservative measures after a reasonable period of treatment.

The air is removed by setting up a water seal drain. This is done by inserting a small catheter into the pleural space and connecting the catheter by a piece of rubber tubing to a water bottle placed on the floor. The bottle is fitted with a two-holed stopper. One of the holes accommodates a short open tube for the escape of air. The other hole transmits the glass tubing to which the rubber tube has been connected; it extends down into the water which half fills the bottle. The tip is left about 3 cm. below the surface of the water. This apparatus permits air to escape from the pleural space.

The usual method of inserting the catheter into the pleural space has been to pass it through a rather large blunt trocar. Recently we have found it more convenient and less traumatizing to use instead the Bardic Intracath, which is used for intravenous infusions. In this device the needle and plastic tubing catheter are incorporated into a single unit (Fig. 1). After the needle has been introduced through the chest wall, the plastic tubing is passed through it into the pleural space and the needle is withdrawn. A small flange on the end of the catheter tightly engages in the needle which then becomes a continuation of the tubing, and the hub may be readily attached to an adapter on the end of a piece of rubber tubing (Fig. 2).

The approach may be made in one of several areas but the site we have commonly used is the second anterior interspace. The skin is prepared and, using sterile technique, the Intracath needle is introduced through the chest wall after preliminary local anesthesia. The plastic catheter is then pushed through the needle to leave a length of 5 to 6 cm. in the pleural space. The needle is withdrawn and pulled to the end of the tubing

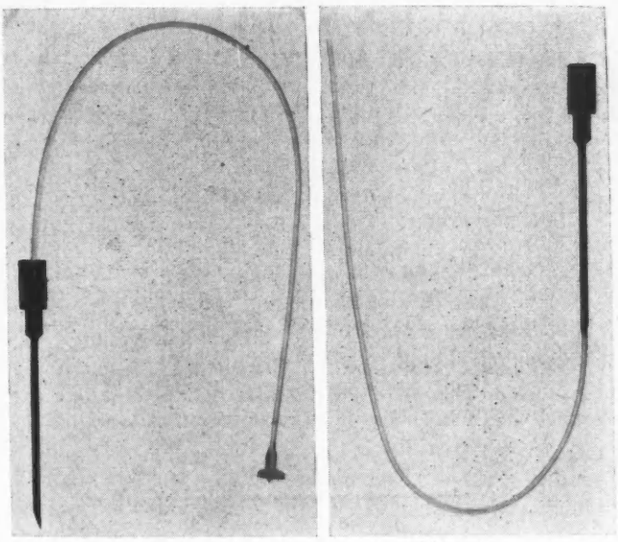

Fig. 1 Fig. 2

Fig. 1.—Needle and catheter when beginning the procedure.
Fig. 2.—Catheter passed through needle.

where the flange is engaged, and the needle is connected to the underwater seal. The plastic tubing is then taped in place so that it will not be pulled out accidentally.

The authors have used this method in eight patients and have found it satisfactory. The catheter has been left in place for periods varying from one to five days and no adverse effect from its use has been noted. For the first patients treated by this method only a medium-sized unit was available but now a large size is available which is more suitable. This consists of a 14-gauge needle, the corresponding catheter lumen being 16 gauge. This size has also been found adequate for taking intrapleural pressure readings, if desired.

It is felt that the use of Intracath as described above is satisfactory. The procedure is easily carried out and is felt to be an improvement over the use of the trocar and rubber catheter.

42 Bellevue Avenue,
Halifax, N.S.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The report of the Winnipeg General Hospital for 1910 shows that there were admitted to the hospital during the year, 5935 patients, who were given 114,938 days of treatment. During the previous year, 5371 patients were accorded 108,659 days of treatment. In the surgical department there were 2295 operations, an increase of 579 over 1909. The *x*-ray department accounted for 3128 treatments and radiographs. The percentage of deaths advanced from 6.63, in 1909, to 6.82. Deducting the number of deaths which occurred within forty-eight hours after admission, the death rate was 4.9, a slight advance, 0.03, over the previous year.—*Canadian Medical Association Journal*, 1: 580, June 1911.

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RECENT CHAPTERS IN THE PENICILLIN STORY

A PREVIOUS editorial in this Journal[1] touched upon the genealogical development of the prolific penicillin family that culminated in the important discovery of the basic nucleus of all penicillins, 6-aminopenicillanic acid (6-APA). In 1950, Sakaguchi and Murao,[2] in Japan, reported that the penicillin nucleus could be obtained by the action of an amidase on benzylpenicillin (penicillin G), but these experiments were not confirmed and for some time their validity was doubted. In 1953, Kato,[3] also in Japan, suggested that the penicillin nucleus was produced in fermentations with *Penicillium chrysogenum* to which no side chain precursor had been added. The first independent announcement of the existence of 6-aminopenicillanic acid was presented in 1958 by Sheehan,[4] as the culmination of an extensive series of investigations. While Sheehan's work constituted a significant contribution to synthetic organic chemistry, it involved a number of stages in which the yields of 6-APA were not high and it did not provide a convenient or practical method for production of large quantities of this substance. Large-scale manufacture of 6-aminopenicillanic acid became possible with the discovery by Batchelor *et al.*[5] that it could be isolated in crystalline form from fermentations of *Penicillium chrysogenum* to which no side chain precursor had been added. More recently, amidases that catalyse the hydrolytic removal of the side chains from penicillins, resulting in the formation of 6-APA, have been shown to exist in a variety of micro-organisms.[6]

While 6-aminopenicillanic acid itself has a very low antibacterial activity, it can be readily treated by the synthetic combination of an almost limitless number of organic materials with its side chain, to yield a tremendous list of additional penicillins with a wide variety of individual properties. Several thousand new penicillins have been obtained in this way and three of these have already been introduced in clinical practice. The first such product, *a*-phenoxyethyl penicillin or phenethicillin, is relatively well absorbed from the gastrointestinal tract and is effective when administered orally. Although initially phenethicillin was hailed with considerable enthusiasm, subsequent evidence has cast doubt upon the major claims for its superiority over benzylpenicillin (penicillin G) and phenoxymethyl penicillin (penicillin V). The second synthetic product of 6-APA, in the form of 6-(2,6 dimethoxybenzamido) penicillanate monohydrate, or methicillin, has more interesting properties and has withstood the test of time in a somewhat more encouraging manner. Because of its ability to resist hydrolysis by the enzyme penicillinase which is produced by certain strains of staphylococci, methicillin is therapeutically effective against these organisms, which are resistant to the antibiotic effects of other penicillins. Unfortunately the property of penicillin resistance on the part of staphylococci and other micro-organisms is a complex phenomenon which apparently involves a factor or factors in addition to the penicillinase mechanism, since certain organisms that do not produce this enzyme may still possess the ability to resist the action of penicillins. The possibility of emergence of staphylococcal strains resistant to even the new penicillinase-insensitive penicillins has been borne out by subsequent observations that several strains of *Staphylococcus aureus* have developed resistance to methicillin after passage through repeated cultures in contact with this antibiotic.[7-10] In addition, naturally occurring methicillin-resistant strains of *Staph. aureus* have also been reported.[11-13] The antibiotic-resistant properties of such strains are apparently not related to their production of penicillinase, since there is no evidence of methicillin destruction in cultures of these organisms. Despite these disturbing developments, methicillin remains a most useful agent for the treatment of staphylococcal infections that are resistant to the earlier penicillins and other antibiotics.

The latest model to roll from the 6-APA production line is *a*-phenoxypropyl penicillin, designated by its manufacturer as PA-248, a product that is apparently efficiently absorbed after oral administration, and possesses the ability to resist the action of staphylococcal penicillinase. The potential of this new antibiotic has been assessed by one group of investigators,[14] in studies of its serum levels after oral administration, by means of (1) determination of the weight of antibiotic per unit volume of serum, and (2) estimation of the antibiotic activity of serum samples, expressed as the number of international units of activity in terms of a standard, or reference antibiotic, in this case benzylpenicillin (penicillin G). These *in vitro* studies prompted the following observations by the authors of this report: (1) Because the minimal inhibitory concentrations (M.I.C.) of phenethicillin and PA-248

were two to four times greater than those of penicillin V against penicillin-sensitive staphylococci, these three orally administered penicillins will probably be equally effective against infections caused by such organisms. (2) Against streptococci, the M.I.C.'s of all orally administered penicillins are roughly equal. Because higher blood levels are achieved with PA-248, it will likely be more effective against streptococcal infections than either phenethicillin or penicillin V. (3) Against Gram-negative organisms penicillin G is the most active, followed in order by penicillin V, phenethicillin and PA-248. (4) Against penicillin-resistant staphylococci PA-248 was considered to be more effective than phenethicillin, which in turn was more active than penicillin V, and since PA-248 produces higher blood levels it was suggested that it will be the least likely of the oral penicillins to permit emergence of resistant staphylococci.

A second investigation,[15] comparing the *in vitro* activity of *a*-phenoxypropyl penicillin (PA-248) against penicillinase-producing staphylococci, with the activities of penicillin G, penicillin V and phenethicillin, was interpreted as indicating that PA-248 was less sensitive than the other penicillins to the action of staphylococcal penicillinase. Of significance in this report was the observation that *there was a considerable difference in activity ratios of the various penicillins against different strains of staphylococci, due to wide fluctuations in sensitivity of different strains of this organism to PA-248*. Despite this variability it was stated that PA-248 usually inhibited at lower concentrations than the other orally administered penicillins under the conditions of this test.

From a small-scale preliminary clinical study,[16] it was reported that five cases of pneumonia due to infection with penicillin-resistant staphylococci "resolved clinically, bacteriologically and constitutionally" when treated with PA-248, while pulmonary infections caused by penicillin-sensitive organisms responded as well to PA-248 as to penicillin V.

Not altogether unexpectedly, in less time than it takes to say "6-(2,6 dimethoxybenzamido) penicillanate monohydrate", the validity of these claims on behalf of PA-248 was disputed in a series of communications appearing in that hallowed forum of British medical opinion, the *Letters to the Editor* columns of the *Lancet*.[17-19] So the controversy, claims and counter-claims over the latest blessed event in the penicillin family have begun. As experience has long-since shown, the real value, limitations and hazards of *a*-phenoxypropyl penicillin, like those of any other antibiotic, must await the test of time.

Meanwhile, in their ivory laboratories, remote (we hope) from commercial furor, the research workers continue to pry into the private lives of innocent moulds and fungi in their quest for new and better antibiotics. Already, their discovery that quite extensive changes can be made in the penicillin molecule without virtual destruction of its antibacterial activity raises the hope that further progress in this field is possible. Antibacterial activity and resistance to penicillinase are not the only properties that are of interest in this connection. It has been suggested, for example, that a substance with low antibacterial activity but high resistance to staphylococcal penicillinase, if it combined strongly enough with the penicillinase, might protect other penicillins from the action of the enzyme, *in vitro*. Also, an antibiotic with limited resistance to penicillinase would be more effective if it failed to induce formation of that enzyme by staphylococci than if, like penicillin G and methicillin, it stimulated penicillinase production by these organisms. The finding of antibiotics with such properties remains a reasonable possibility.[6]

In the last few years much has been learned concerning the effects of modifications of penicillin structure on antibacterial activity, ability to combine with penicillinase, and ability to stimulate production of penicillinase. Changes in one of these characteristics are apparently not necessarily accompanied by changes in the others. It is also apparent that the action of penicillinase on different penicillins varies with the source of the enzyme. More information is now required concerning the variations of these properties with alterations in penicillin structure, and concerning the exact structural site of enzymic activity within the penicillinases. With such information it may become possible to predict the structures of new compounds with even more useful biological properties.[6]

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LEUKEMIA MORTALITY TRENDS

THOSE indefatigable statistical sleuths, Court Brown and Doll, have been at it again, as evidenced by their recently published analysis of leukemia mortality rates among children and young adults under the age of 30 years, in England and Wales during the period 1911-1959 (*Brit. M. J.*, 1: 981, 1961). They also examined similar data from other countries over a shorter period and found that since 1911, except in the age groups

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0-4 years and 15-19 years which have shown no increase in leukemia mortality in the last 10 years, the mortality rate has increased fairly steadily with an increment of approximately 4% to 4.5% per annum in each five-year age group and in each sex. In the first year of life the mortality rate was similar in both sexes but at subsequent ages the male mortality was higher and showed a small peak at ages 15-19 years. Among girls a similar peak was seen less often. Since 1920 a childhood peak mortality at ages 2-3 years has been observed and since 1940 this has become more pronounced. Similar mortality rates, but at a higher level, have been observed in the white population of the United States; but no peak in childhood mortality has been evident in the non-white population of the United States or in Japan. In the period 1945-59, estimated mortality rates in England and Wales showed that: (1) in acute lymphatic leukemia there was a maximum rate at age three years in both sexes and this subsequently fell to a minimum at ages 25-29 years with only a slight check at ages 15-19 years; (2) in acute myeloid leukemia there was less variation in mortality rates, but there were still two peaks at ages 2-4 years and 15-19 years; (3) in both types of chronic leukemia the mortality was low throughout the age range studied but there was evidence of an increase in mortality from chronic myeloid leukemia above the age of 20 years. In this same period, 1945-59, analysis of the 50 known cases of leukemia in association with mongolism indicated that the increased risk of acute leukemia in mongolism affected all types of the disease commonly observed in childhood. Evidence obtained from a study of records of identical twins suggested that the development of leukemia in identical twins was uncommon.

A detailed study of the transient rise of the leukemia mortality rate during adolescence, recently reported by Lee (*Brit. M. J.*, 1: 988, 1961), revealed that in England and Wales, Scotland, Canada and the United States, the decline of death rate with age stopped at about age 13 in males, rose to a new peak at 17 years and thereafter fell continuously until the late twenties. There was a similar but less marked trend in females. The data indicated that these extra cases in male adolescents were concentrated among the acute myeloid leukemia patients who had histories of less than two months between the reported onset of symptoms and admission to hospital.

BROTHER TIMOTHY JOINS THE JOURNAL

ON June 1 a neatly dry-cleaned and crisply pressed welcome mat was spread at the portal of C.M.A. House in recognition of the arrival of a distinguished addition to the editorial staff in the person of Dr. John O. Godden, newly appointed Associate Editor of C.M.A. Publications.

Born in Halifax, Nova Scotia, on September 22, 1921, John Godden obtained his elementary and high school education at New Glasgow, N.S. In 1940 he embarked upon an interlude devoted to the study of Commerce at Dalhousie University. After serving with the Canadian Army in the Royal Canadian Infantry Corps in 1944 and 1945, he completed his pre-medical education at Dalhousie and McGill Universities in 1945 and 1946, enrolled in the Faculty of Medicine at Dalhousie in 1946 and graduated M.D. C.M. in 1951. From 1952 to 1955 Dr. Godden pursued his postgraduate training in internal medicine at the Mayo Clinic and in 1955 the degree of M.Sc.(Med.) was conferred upon him by the University of Minnesota. After completing his postgraduate studies at the Mayo Clinic he joined the Faculty of Medicine at Dalhousie University on his appointment as Associate Professor in the Department of Preventive Medicine. Awarded a McLaughlin Travelling Fellowship, Dr. Godden spent the year 1956 in further peripatetic postgraduate study in the area of medical education and after returning to Halifax he qualified for certification by the Royal College of Physicians and Surgeons of Canada as a specialist in internal medicine, in 1957. In that year he was also appointed as Assistant Physician on the staff of the Victoria General Hospital, Halifax, and the Nova Scotia Tumour Clinic.

During the course of this congested postgraduate schedule Dr. Godden married the former Barbara Jean Fullerton of Pictou, Nova Scotia, and became the proud parent of two sons and two daughters.

Beyond his background of training and experience in academic, clinical and preventive medicine, Dr. Godden brings to the C.M.A. editorial staff the fruits of several active years engaged in the various, and at times nefarious, pursuits of medical journalism. With a considerable list of personal publications to his credit he has served as an Associate Editor of the *Nova Scotia Medical Bulletin* from 1957 to 1960 and as the Bulletin's Acting Editor during a period in 1960 and 1961. His facile pen, crusading spirit and refreshing wit, as revealed in the epistles of Brother Timothy, are familiar to all who have read that remarkable feature section of the *Nova Scotia Medical Bulletin* that appears under the heading of "Hay for Hobby Horses".

In welcoming this talented recruit to the editorial staff we look forward to his long and productive association with the publications department of the C.M.A.

CHANGE OF ADDRESS

Subscribers should notify the Canadian Medical Association of their change of address one month before the date on which it becomes effective, in order that they may receive the Journal without interruption. The coupon on page 37 is for your convenience.

LETTERS TO THE EDITOR

REMUNERATION OF DOCTORS BY SALARY

To the Editor:

I have read with interest the letter from Dr. J. A. McMillan (*Canad. M. A. J.*, 84: 799, 1961) concerning "Remuneration of Doctors by Salary". As the "new Canadian doctor from Saskatchewan" to whom he refers, I feel that I must, with great respect, take issue with some of his statements.

It is true that it would be false logic to argue that, since "25 to 30% of doctors now *de facto* work for salaries; *ergo*, all doctors could work for salaries". This is not the argument that I personally have put forward as my reason for supporting a salaried health service, either on television or elsewhere.

Unfortunately, Dr. McMillan goes on to make certain statements which in their turn do not stand the light of careful scrutiny.

For example, he says that "doctors who render personal health services do not work for salaries". In the Mental Health and Tuberculosis Services of this province and others, there are many physicians on full-time salary, as there are many surgeons, internists and others in the medical schools and clinics of Canada and the world. This, as is well known, is also the personal preference of many physicians in privately operated group practices. Presumably Dr. McMillan would agree that all these people are rendering personal health service.

Dr. McMillan then appears to argue that if doctors are paid on salary (by governments? by private plans? by clinics?) there can be no freedom of choice. I should be interested to hear the steps in logic that lead him to this remarkable conclusion.

He also infers that fee-for-service is the only method of paying doctors which enables them to be remunerated "according to the quality of care [they are] competent to give and to the quality of care medically necessary to the patient's problem". I am unable to see how the way in which a man is paid can affect what he is *competent* to do, or how a method of payment can affect the quality of what people *need*. I am not aware of any scientific studies which show that physicians paid on fee-for-service actually do better work than those who are not. I am aware of some studies which infer that the fee-for-service method hampers physicians in giving their best.

The rigid adherence of our profession to the fee-for-service principle is damaging to our reputation in the eyes of the public. Whether or not they are right in doing so, they see it as representing an undue concern with how much we earn. They also consider it an unrealistic and out-of-date stand in a society which has moved steadily away from "piece-work" methods of payment in so many trades and professions.

Dr. E. Kirk Lyon, the Association's distinguished former Deputy to the President, was statesman-like and far-seeing when he said (*Canad. M. A. J.*, 83: 628, 1960), "It is open to question whether in all circumstances the fee-for-service principle can be defended as the only way we, as a profession, can be remunerated for our service." Dr. Lyon also said that, under the fee system, "the doctor who is physically capable of performing the greatest number of services and not necessarily the best services, is the one whose remuneration becomes the greatest . . . furthermore, it is highly doubtful whether many of the new and complicated procedures, which require the teamwork of many highly trained individuals, can ever be paid for in any other way than on a unit basis."

These are wise words. It is also doubtful whether the element of continuity of care, basic to our modern concept of good medical practice, can ever be adequately promoted under this system. Fee schedules under-value preventive and over-value treatment services, out of line with current trends in medicine and with the relative worth of these two types of service to many patients.

The fee-for-service method of payment also gives the physician and those concerned with the administration of any program an unnecessary mass of burdensome and expensive paperwork. Not only must records of the services given to each patient be kept as for professional reasons but also itemized bills specifying the services given and the patients treated must be made out.

Under the fee-for-service system, the temptation towards the promotion of unnecessary use of services is also exaggerated. Although we know that overservicing is the responsibility of a very small group indeed, its results are extremely expensive to any medical care plan.

It would be foolish to argue that the salary method of paying doctors, or the capitation method, or the fee-per-case method, will any one of them provide a solution to all the problems of medicine in modern society. It is highly desirable that members of the medical profession should examine this matter with that degree of objectivity, patience and impartiality which characterizes their examination of a problem at the bedside or in the laboratory.

Dr. McMillan accuses me of using an argument which I did not use, and he calls that argument "nefarious and insidious". He says that "all doctors should be prepared to refute it". If I had put forward this particular argument as the main one for supporting a salaried service (which I did not), and were Dr. McMillan's own arguments based on the facts (which they are not), he would indeed have good reason for concern. It is surely a matter of much greater concern that this, like all other aspects of the planning of medical care insurance, should be studied in full objectivity and with a knowledge of the facts.

ALEXANDER ROBERTSON, M.D.,
Professor of Social and
Preventive Medicine
University of Saskatchewan,
Saskatoon, Sask.

To the Editor:

Professor Alexander Robertson still hasn't his "de facto's" and his "ergo's" straight. Dr. McMillan does not "presumably agree" that doctors in mental health and tuberculosis services in any province are "rendering personal health services". They render services to

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persons. This is correct. However, government monopoly decrees to whom such persons must go and under what conditions. Government controls the quality and the quantity of services such patients receive and also controls the amount of money that must be spent on their care. Such is in no way therefore a personal health service.

In his consistent form of sophistry Professor Robertson groups such doctors with "surgeons, internists and others in medical schools and clinics in Canada and the world" who receive salaries. No such comparison exists. Such men do not work under a government monopoly; they control their own destinies and conditions of practice; they have some voice in their departments and clinics and are not subject to the limitations of government intervention. They are free as persons, as citizens and as doctors. They are free to choose their political and other persuasions. They are not required as are the doctors working in the Cottage hospital service in Newfoundland to take oaths of loyalty and secrecy before they receive their remuneration.

Professor Robertson is "unable to see how the way a man is paid can affect what he is competent to do". With this I agree. Perhaps he might be able to see that what a doctor is paid should be proportionate to the kind and degree of service he gives to his patient. This further ensures the patient's right to some voice in his choice of doctor and service.

No, Professor Robertson, fee for service is not a dogma as you suggest. Ease of payment and billing doesn't interest doctors. You should know this. Fee for service does not facilitate over-servicing but very definitely capitation and salary do promote underservicing and lack of responsibility on the part of the doctor.

Objectivity, according to Webster, concerns "expressing facts without distortion from one's personal feelings or prejudices". Professor Robertson's history and practice hardly qualify him as objective about what he says and writes. He, more than most, should know that the patient always suffers when his treatment and care depend on government money. No government will ultimately spend enough to provide the high-quality and readily available care patients want and look for. Only the patient and his doctor can ensure these necessary qualities. That our confrères in government services at present have so efficiently carried out their services is a tribute to their personal devotion to the care of their patients in the limited fields in which they now work and is not at all related to the fact that many of them are on salary. Most of them admit that to extend this type of practice to areas of personal and individual medical service would only result in an inferior quality of service and hasten the development of a much less qualified profession.

The doctors of Canada have helped to develop a very high standard of both general and specialty practice. I feel quite certain that they are equally capable and willing to develop the best methods of financing medical care for Canadians and for those recently welcomed to our country without the necessity of the state sacrificing the liberty of its citizens to the god of economy or political theory.

I am glad that Professor Robertson reads the words of Dr. Lyon. This is indeed encouraging. If he reads far enough, there is hope that his public expressions will be more enlightened.

J. A. MCMILLAN, M.D.
200 Queen Street,
Charlottetown, P.E.I.

THE INDUCTION OF LABOUR

To the Editor:

I shall be grateful if you will allow me space to comment on a recent editorial in the *C.M.A. Journal*, entitled "The Induction of Labour".[1] In this editorial it is stated that the intravenous infusion of oxytocin "usually consists of five international units in 500 c.c. of solution given at a rate of 15 to 20 drops per minute."

This is dangerous teaching, and is responsible for the occasional tragedy which occurs when oxytocic infusions are given. I would direct attention to the writings of Theobald,[2-5] one of the pioneers in the use of this method of inducing labour, who in the course of 11 years has had remarkably few complications. He believes that this is due entirely to the use of very dilute solutions; he begins with an infusion containing ½ unit in a 500-c.c. drip-bottle administered at a rate of 20 drops per minute—precisely one-tenth of the strength recommended in the Journal's aforementioned editorial —and he notes that 88% of his patients were delivered with less than 1 unit in 500 c.c. at 20-40 drops per minute, so that stronger solutions are only rarely required.

The drug manufacturers are partly to blame for the administration of the larger doses of oxytocics; Pitocin, for example, is supplied in ampoules containing five units in 0.5 c.c. or 10 units in 1.0 c.c., and the measuring of ½ unit of Pitocin requires much juggling with a tuberculin syringe. The newer synthetic oxytocin, Syntocinon, is supplied in smaller dosages (2 units in 2 c.c.), but even this is too great.

One of the dangers of the oxytocic drip is the unreliability of the apparatus in the consistency of the rate of flow of solution, which may alter rapidly with movement of the patient, kinking of the tubing, or apparently from sheer devilment. Such alterations seem to take place just when the doctor supervising the drip is called away to the telephone or leaves the patient for some other purpose; by the time he returns the uterus is in a state of tonic spasm and the damage is done, especially if the solution is a strong one. The only answer to this problem is to employ a mechanical pump which can be regulated to supply accurately a certain volume of fluid in a given time, although with the use of weak oxytocic solutions the danger is minimal.

I think that all obstetricians will wholeheartedly endorse the criticism of the intramuscular injections of oxytocic drugs to induce labour. At the 15th British Congress of Obstetrics and Gynaecology in 1959, Wrigley[6] stated, "This Congress would render no disservice to the community if it declared its complete condemnation of the practice of the administration of Pitocin by the method of repeated intramuscular injections."

H. M. GOUGH, M.B., B.Ch., M.R.C.O.G.

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MEDICAL NEWS IN BRIEF

SMOKING HABITS OF SCHOOL CHILDREN IN AN IRISH COMMUNITY

A survey of the smoking habits of 2706 school children was conducted in Westmeath County, Eire, from September 1959 to February 1960 by means of a questionnaire. The children ranged in age from 10 to 20 years; over half were between 12 and 15. M. P. Flynn (*J. Irish M. A.*, 48: 87, 1961) reports that 27% of the boys and 7.5% of the girls were smoking one cigarette or more per week at the time of the survey. In addition, 17% of both sexes smoked an occasional cigarette. Twenty-nine per cent of the boys and 44% of the girls had never smoked. At 11 years of age 12.8% of boys and 2.6% of girls smoked one cigarette or more per week and at 15 years the incidence was 28.8% and 10.7% respectively. The sex ratio was 3 or 4 boys smoking to each girl smoking.

Many children, particularly boys, smoked their first cigarette before their tenth birthday. Smoking was almost twice as frequent among children where both parents smoked than where neither smoked. Seventy-five per cent of the fathers and 43% of the mothers smoked.

Among the measures suggested by the author to reduce cigarette smoking are strict enforcement of the law prohibiting the sale of cigarettes to children under 16 years; advising those who must smoke to change to a pipe or cigars; alteration of excise duty in favour of pipe and cigar tobacco; and restrictions on the advertising of cigarettes, but not of cigars and pipe tobacco.

EXPERIMENTAL STUDIES ON CEREBRAL CORTICAL BLOOD FLOW

The first reliable measurements of cerebral blood flow were described by Kety and Schmidt in 1945, using low concentrations of nitrous oxide as an indicator. This method depends on the premise that if a gas, easily diffusible and physiologically inert, is inhaled, the rate at which its concentration in the blood of cerebral veins approaches that in arteries is a function of the blood flow through the brain. The accuracy of this method can be increased by using the beta-emitting isotope Krypton. Since this method depends on equilibration of the gas concentrations in the brain tissue and the cerebral venous blood, measurements must be continued for at least 15 minutes. It is therefore unsuitable for measuring rapid changes in cerebral blood flow.

In 1956, Lewis *et al.* reported a modification of Kety's method, substituting the gamma-emitting isotope Krypton^{79} for nitrous oxide and measuring continuously the amount of gas in the brain by means of an external scintillation counter. Combined with arterial and cerebral venous blood analysis, this permits semi-continuous measurements of total cerebral blood flow. It is a technically difficult procedure, however, and the accuracy of the results may be impaired by the presence of any Krypton^{79} in extracerebral tissues.

Until recently therefore, there was no satisfactory method for rapid estimations of cerebral blood flow. In 1955, however, Kety described a technique for determination of regional blood flow to the brain, which was based on the rate of uptake by brain tissue of the radioactive indicator, I^{131}-antipyrine, following its injection into the blood stream. The radioactivity of the brain was measured from autoradiographs of frozen brain slices. Later, a technique for measuring radioactivity of the brain by external counting with a Geiger counter mounted over the exposed brain cortex, eliminated the necessity of obtaining brain slices. Krypton^{85} is used as the indicator and the initial slope of a semilogarithmic graph of the clearance curve of the isotope from the brain tissue is used to calculate the blood flow through the brain cortex.

Recent experimental studies of cortical blood flow in dogs have been carried out by Harper, Glass and Glover, at the Glasgow Royal Infirmary (*Scottish M. J.*, 6: 12, 1961). These workers observed that the cortical blood flow is very sensitive to changes in arterial pCO_2. Raising the pCO_2 from 30 to 70 mm. Hg resulted in an approximate doubling of the flow. The results of repeated estimations under constant conditions using the technique described above, showed a small standard deviation. The mean value for cortical blood flow in nine dogs was 0.99 ml./g./min. There was little difference in blood flow through the frontal, parietal and occipital cortex.

WATER RETENTION DUE TO HYPOKALEMIA

Hypokalemia is described as one of the less well-known causes of generalized edema, in a recent report by Hadorn (*Schweiz. med. Wchnschr.*, 91: 47, 1961). This was first reported in two patients who developed edema after the excessive use of laxatives. The proof of cause and effect was the disappearance of water retention after correction of the hypokalemia. In the last seven years several authors have reported similar observations. In such cases the edema is thought to be due to sodium retention secondary to lowering of serum potassium. Hadorn refers to experiments carried out by Muller in Geneva, in which restricted potassium intake resulted in reduced excretion of aldosterone in normal persons. Concomitant with this he observed a progressive sodium retention, which strongly suggested that potassium depletion causes retention of sodium by the renal tubular cells, and that a drop of aldosterone secretion is a protective mechanism against sodium retention. The observation that hypokalemia can lead to edema may throw some light on the still poorly understood pathogenesis of hunger edema. Here, hypoproteinemia is an important factor but not the sole causative mechanism, as hunger edema can exist without hypoproteinemia and not all persons with hypoproteinemia develop edema. In some cases, hunger edema disappears in spite of persistence of hypoproteinemia. The frequent appearance of hunger edema in concentration camps in connection with epidemic diarrhea also suggests that hypokalemia may have been the determining factor in the production of water retention. This is the more impressive as it is natural to assume that diarrhea would counteract the tendency to water retention.

(Continued on advertising page 32)

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MEDICAL MEETINGS

EIGHTY-FIRST ANNUAL MEETING: ONTARIO MEDICAL ASSOCIATION

(CONCLUDED)

General Session, Thursday Morning, May 11

The general session on surgery was chaired by Dr. R. C. Laird, Surgeon-in-Chief, Toronto Western Hospital, and Professor of Surgery at the University of Toronto. The first paper, entitled "Solitary Lung Nodules", was presented by Dr. G. H. C. Joynt of the surgical staffs of Toronto Western and Sunnybrook Hospitals. Dr. Joynt discussed the major differentiating features and general principles of management of solitary nodular lesions in the lung as encountered in a series of 100 patients. Forty-three of these had primary pulmonary carcinoma, six had secondary carcinoma of lung, 39 had granulomatous lesions, nine had benign tumours, two had benign pulmonary cysts and one a loculated hematoma. In the discussion following Dr. Joynt's presentation, Dr. A. Grace of London stressed the importance of maintaining a high index of suspicion regarding the diagnosis of primary carcinoma in such cases, since it is a common cause of solitary nodular lesions of the lung, as noted by Dr. Joynt, and it cannot be ruled out definitely until microscopic examination of the lesion has been performed. It was observed that laminagrams are of some value in preoperative investigation in such cases, and that calcification of the lesion, particularly laminar calcification, is suggestive evidence that the lesion is benign. Adenocarcinoma tends to occupy a peripheral site, to predominate in women, to spread by the blood stream and to present as a solitary lesion in many instances. This type of carcinoma tends to be associated with better results from lobectomy than do other malignant pulmonary tumours. One-third of the carcinomas in Dr. Joynt's series were adenocarcinomas.

Dr. W. A. Brown of the surgical staff of Toronto Western Hospital and the University of Toronto presented the second paper of this session, on the subject of "Benign Epithelial Tumours of the Parotid Gland", based on a study of 41 lesions of this nature. These were classified as mixed tumours of the parotid (the most common type), Warthin's tumours (papillary cystadenoma lymphomatosum), adenolymphomas, benign lymphoepithelial lesions, mucoepidermoid tumours, acinic cell adenomas and simple cysts. Mixed tumours are characteristically ovoid and sharply demarcated in the gross, and microscopically present a pleomorphic picture which includes areas of cartilage and pseudocartilage. Warthin's tumours tend to occur in or near the cervical pole of the gland. Microscopically they exhibit epithelial papillary folds with an underlying lymphoid component which may even assume the form of lymph follicles. Cystic areas containing honey-like fluid are a common feature of this type of parotid tumour, which predominates in men. Benign lymphoepithelial lesions present inflammatory as well as neoplastic features. They may be discrete or diffuse and occasionally are bilateral. They are more common in women, are usually soft in consistency and microscopically reveal epithelial components scattered throughout a mass of lymphoid tissue. This type of lesion may be treated by radiation therapy rather than by surgical excision. Mucoepidermoid tumours are difficult to differentiate from mixed tumours. There is some question as to whether this lesion is actually neoplastic in nature. Acinic cell adenoma is a rare parotid tumour that occurs predominantly in women. Clinically it cannot be differentiated from the mixed tumour. It is a soft tumour consisting of solid cellular aggregates held together by a fine vascular stroma. Simple cysts are benign lesions but biopsy is required to establish their diagnosis.

The investigation of parotid tumours should usually include plain roentgenographic studies. Dr. Brown expressed the opinion that sialograms are of very little use as a general rule and that biopsy is the most important aspect of investigation of any parotid tumour. He discussed the surgical techniques advocated for the various aforementioned lesions and commented on his preference to operate with the patient in a hypotensive state to reduce postoperative reactive edema. In discussing Dr. Brown's paper, Dr. Robert Janes of Toronto stressed that all patients with parotid tumours should be subjected to operation as the only definite way to rule out or establish a diagnosis of malignancy. Dr. Janes also commented on the difficulty in differentiating parotid tumours from cervical lymph node lesions in many cases.

Dr. J. Ross Fleming, Attending Neurosurgeon, Toronto Western Hospital, and Clinical Teacher in Surgery, the University of Toronto, delivered a modest but impressive account of "The Results of Surgical Treatment of Parkinson's Disease", based on a series of 24 patients with disabling parkinsonism treated by operative procedures over the past four years. At first, selection of patients for this form of treatment was confined to those who were relatively young, with unilateral tremor and/or rigidity and possessed of some potential capacity for occupational rehabilitation. Those who appeared to be incurable invalids and those with evidence of mental deterioration were excluded. It was soon decided that these criteria were too exclusive and selection of patients for operation was made on a more liberal basis. Most of the patients in Dr. Fleming's series were in the 50-65 year age group. Bilateral disease, *per se*, is not an absolute contraindication to surgical treatment, but operation confined to the more severely affected side is preferable since bilateral operation leaves considerable residual disability largely due to severe lethargy. Dr. Fleming stressed that no surgical procedure devised to date (which he described as "punching holes in the thalamus") provides a definitive cure of Parkinson's disease, but such measures may result in worthwhile relief of tremor, rigidity, bradykinesis and the impairment that these disorders cause in speech, movement and general functional capacity, in about one-half to two-thirds of cases. The method by which surgical lesions of the thalamus and globus pallidus produce clinical improvement is not understood. Of the 24 patients in Dr. Fleming's series 17 showed some improvement after operation, four were unimproved and three were worse. There was one fatality in this group. In four, repeat operation with enlargement of the initial lesion produced marked and

lasting improvement. Five were subjected to bilateral operations. In these, the second operation did not often result in any striking additional benefit and it was frequently followed by disabling lethargy. Some patients in this series had evidence of diffuse cerebral degeneration as suggested, for example, by pyramidal tract signs, after operation. Postoperatively, transient field defects and hemiparesis were commonly encountered. From the point of view of technique, the surgeon's target is the thalamus and globus pallidus, from which site a section of brain tissue is removed by a wire loop with the patient under local anesthesia. Localization of the operative site is facilitated by a specially designed, expensive stereotactic apparatus. The surgical procedure itself is a fairly simple one, throughout which the patient must be awake to permit reliable testing of power, tremor and rigidity as the operation proceeds. This is essential since the internal capsule is so close to the operative site and damage to the capsule must be avoided. Dr. Fleming concluded this highly interesting presentation with impressive "before and after" motion pictures illustrating the preoperative disability of several patients and the response following operation. In the discussion of this paper, Dr. T. Morley of Toronto commented that the surgical treatment of Parkinson's disease has provided one of the most exciting and enlightening advances in our knowledge of the pathology, pathogenesis and treatment of diseases of the nervous system in recent years. He noted that Dr. Fleming had performed the first neurosurgical operative treatment of a patient with Parkinson's disease in Toronto. Dr. Morley also commented on the changing concepts of selection of patients for operation. At first only those with tremor were considered suitable, then the criteria for selection were extended to include those with rigidity, and now operative treatment is performed on patients with no manifestations other than extreme and disabling immobility without tremor or rigidity. The mechanism of production of this latter type of manifestation is not understood.

After a brief recess period the session resumed with a report on "The Management of Surgical Lesions of the Pancreas" by Dr. J. F. R. Mills, Associate Professor of Surgery, the University of Toronto, and Senior Surgeon at Toronto General Hospital. Dr. Mills observed that during the past 25 years there has been a large volume of laboratory and clinical research on pancreatic function and during this period surgeons have become more bold and accomplished in various operative procedures on this organ. Nevertheless, real progress in treatment of its disorders has been slow. There is, however, an increasing awareness of the many problems involved in this field, and further advances in such treatment may be expected in the future. There is general agreement that the treatment of acute pancreatitis should be non-operative but that operation is indicated for the treatment of its complications. Conservative treatment consists of constant gastric suction; adequate fluid replacement, administration of antibiotics and of serum albumin and blood if indicated. The fluid and electrolyte balance and hematocrit readings should be followed carefully. Intravenous calcium gluconate is indicated if hypocalcemia develops. Anticholinergic drugs may be used in an attempt to depress pancreatic function. The value of corticosteroids is uncertain. In late stages of the disease it is important to recognize complications and treat them promptly. If pancreatic necrosis, sepsis or cyst formation develops, the organ should be drained. Postoperative pancreatitis is a condition that occurs most frequently after operations on the duodenum, stomach, biliary tract and pancreas, though it may follow any abdominal operation. This disorder should be suspected in any patient with serious intraperitoneal distress in the immediate postoperative period. It is treated in the same way as acute pancreatitis in a patient who has not had an operation.

The treatment of chronic relapsing pancreatitis is the subject of considerable diversity of opinion. Many procedures have been advocated but their results leave much to be desired. About 55% to 60% of cases of pancreatitis are associated with gallstones. Dr. Mills recommended the treatment of such cases by cholecystectomy, exploration of the common bile duct and, if the common duct sphincter is tight, sphincterotomy and duodenotomy. Pancreatography is of questionable value but Dr. Mills observed that this procedure had recently been instrumental in providing the diagnosis of two pancreatic pseudocysts, in his experience, which would otherwise have escaped diagnosis. In patients with an isolated stricture in the pancreatic duct distal to the ampulla, retrograde pancreatico-jejunostomy is advised. Obstruction at the ampulla is treated by sphincterotomy only. With multiple duct strictures, side-to-side anastomosis of that portion of the duct to the duodenum is advocated. Choledocho-duodenostomy should probably be reserved for those with common duct obstruction. Pancreatic resection as advocated by Cattel is a major procedure for benign disease. Once-popular sympathectomy and vagotomy appear to have fallen into disrepute. In brief, no single operation is successful in all cases of chronic pancreatitis; the operation must be selected to meet the needs of each individual case.

Pancreatic pseudocysts followed acute pancreatic necrosis or pancreatitis in 21 of the 23 cases reviewed by Dr. Mills at the Toronto General Hospital. The remaining two followed operations on the pancreas or stomach. Simple drainage of these is the treatment of choice in cysts of short duration, with a well-organized wall, if infection is present, or if the patient is seriously ill. Marsupialization is now rarely practised. Excision of cysts and partial pancreatectomy is indicated if the cyst is neoplastic. Rarely, simple cysts in the tail of the pancreas are suitable for excision. Sphincterotomy is indicated if the cyst is a complication of relapsing pancreatitis. Anastomosis of the cyst to the stomach or to a defunctioned loop of jejunum is a currently popular procedure.

The features of 25 cases of islet cell tumours of the pancreas encountered at Toronto General and Sunnybrook Hospitals were reviewed. In addition to recognizing Whipple's triad of diagnostic criteria, one must be certain that the patient has not been giving himself insulin, in all cases of suspected islet cell adenoma. Twenty of these 25 tumours were benign and all but one of the benign lesions were functioning adenomas. The tumours were generally fairly evenly distributed throughout the pancreas. The operative procedures employed in these cases were discussed.

Carcinoma of the head and peri-ampullary region of the pancreas, treated by radical resection, has a high mortality and morbidity but for lesions of the ampulla of Vater, duodenum and lower end of the common bile duct, radical pancreatico-duodenectomy gives better results. For palliative procedures to relieve

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obstructive jaundice associated with pancreatic carcinoma, a long-loop cholecysto-jejunostomy with entero-enterostomy, with or without gastroenterostomy, gives the best results.

Ulcerogenic tumours of the pancreas, the Zollinger-Ellison syndrome, is an entity comprising fulminating and frequently fatal peptic ulceration with excessive gastric secretion, refractory to ordinary medical and surgical therapy, accompanied by non-beta cell tumours of the pancreas. The peptic ulceration may involve the stomach, duodenum or jejunum. A high proportion of the pancreatic tumours in such cases are multiple and the majority reported by Ellison were malignant. Their association with the production of glucagon is not yet settled. This lesion should be suspected in cases of refractory peptic ulceration, and the pancreatic tumour or tumours, if found, should be removed.

The final paper of the general session on surgery, "Surgical Treatment of Hiatal Hernia: Indications and Methods", was presented by Dr. D. B. Effler, Chief of the Department of Thoracic Surgery at the Cleveland Clinic, Cleveland, Ohio. Dr. Effler observed that hiatal hernia is just another form of coelomic herniation. It is unique because the herniated viscus usually is the stomach. The mechanism of herniation is identical to that of most other types of coelomic hernias, a weakening or relaxation of supporting tissues in addition to persistent intra-abdominal pressure. The most common symptom is pyrosis after meals and in recumbency. The complications of hiatal hernia are related also to the gastric mucosa and its ectopic position above the diaphragm. The most frequent complications are ulceration, bleeding and obstruction by stricture at the esophagogastric junction. From the surgeon's point of view there are two basic forms of hiatal hernia: (1) The pulsion type, in which the motivating force is the intra-abdominal pressure exerted against a naturally weak point in the diaphragm. So-called para-esophageal and sliding hernias are included in this group. (2) The traction type, in which the gastric component is drawn into the mediastinum by contraction of the esophagus. This is usually referred to as the short-esophagus type and comprises about 10% of hiatal hernias.

Dr. Effler deplored the welter of confusion that has involved the subject of hiatal hernia as a result of verbose reports by internists, gastroenterologists and radiologists which have submerged the basic problems of this disorder in trivia, irrelevant detail and erroneous concept. The basic problem, he said, is an anatomic derangement; correct this derangement surgically and the problem is solved. Dr. Effler then proceeded to describe how the derangement should be corrected surgically, and how the problem should be solved.

General Session—Friday Morning, May 12

The final general session was conducted in the lachrymose atmosphere engendered by a symposium entitled "The Crying Infant". Chairman of the session was Dr. A. M. Bryans, Professor of Pediatrics at Queen's University and Head of the Department of Pediatrics, Kingston General Hospital. Professor Bryans opened the symposium with a discussion of "Feeding Problems and the Crying Baby". Dismissing the common, "normal" or "physiological" types of crying, he commented on the pattern of almost incessant crying that characterizes the syndrome of infantile colic which is marked by extreme eagerness for feeding, abdominal distension, excessive flatus, somewhat loose stools, and above all, crying as though in pain, with a red face anl legs drawn up. The baby is likely to be a tense, wiggling type of hypertonic infant who may exhibit vomiting, sometimes of projectile type. Constitutional and environmental factors, as well as feeding problems, are involved in this syndrome. The feeding faults in such cases include insufficient feeding leading to hunger; small nipple hole leading to hunger, fatigue, frustration and gas swallowing; allergy; overfeeding; constipation; and excessive carbohydrate. Whatever the basic cause, a vicious circle is established with distension of intestinal loops by gas, crampy pain, crying and more air swallowing.

Hunger is probably the commonest feeding defect associated with infantile crying. Some infants have more rapid gastric emptying than others, some grow more rapidly than others, so some need more calories than others. This need can be met by minor adjustments in the milk feeding and by the use of solid food for bulk as well as calories. Moderate caloric increase, enlargement of nipple holes, frequent burping of the infant during and after feeding and reassurance of the parents are indicated in such cases. There is no sound reason for changing the feeding formula otherwise, though some alteration in the fat content, from full-strength evaporated milk to partly skimmed evaporated milk, or the use of 2% lactic acid milk or full-strength acidified milk, may be tried on an empiric basis. Later, a non-milk formula may be introduced. During such formula alterations phenobarbital, 8 mg. in aqueous solution four times daily before feedings, with or without an antispasmodic such as atropine or homatropine, may be used in an attempt to alleviate the infant's distress. Chloral hydrate, 60 mg. before feedings, or an antihistamine may also be of benefit in some cases, and a pacifier may be used for the first six to eight months. For particularly bad attacks, especially at night, a glycerine or soap stick suppository may provide some relief of distension by inducing the passage of gas.

A small number of infants present a similar clinical picture due to allergy to cow's milk, sometimes accompanied by other allergic manifestations such as infantile eczema or seborrhea. Some of these have a greater tendency to diarrhea than to colic. In such cases it is wise to give the infant a trial on a non-milk feeding if there has been no response to the aforementioned measures. Soy-bean or goat's milk feedings may be used for this purpose and if allergy is the cause of the infant's distress, the result is most gratifying. The value of this procedure can be readily assessed within a week.

Overfeeding is not a common cause of the syndrome of infantile colic. Withholding all carbohydrates for a week or changing the dietary carbohydrate to Dexin (a tapioca product), for example, may be worthy of a trial.

In the occasional severe case of infantile colic, hospital admission for observation and the provision of a brief interlude of peace for the parents may be desirable. Failure to respond to any of these measures requires more detailed investigation to rule out less common but important causes of perpetual infantile crying.

Dr. J. J. Slavens, Clinical Teacher in Pediatrics at the University of Toronto and Assistant Physician in Pediatrics and Neurology at the Hospital for Sick Children, Toronto, discussed "Behaviour Disorders" in

relation to excessive crying in infancy. He pointed out that infants readily learn that crying may be one means by which they can attain reward or attention. Excessive crying, colic, or the hypertonic state of infancy may be defined as that crying which is not alleviated by feeding, holding or other methods to ensure the baby's comfort. Besides the manifestations of colic, restlessness, sleeplessness, irritability and pylorospasm, these babies are extremely tense. Treatment consists of sedation. Several opinions indicate that this group contribute to those who show behaviour problems at older ages. Nothing abnormal is found on physical or laboratory examination. Environmental factors such as confusion, hurry, loud noises, and obvious parental tension or anxiety all contribute to further upset these infants. A baby's first means of communication is by crying. The sooner he learns that his objectives will not be attained by this means, the less likely he will be to use it. Significant behaviour disturbances during the first year of life are relatively infrequent as compared with the second year, for there are comparatively few occasions for conflict between mother and infant in the majority of cases during the early months of life.

Investigation of a baby who cries excessively must include a complete history, with emphasis on the time of occurrence of the crying, its relation to food and excretion. Complete examination with whatever tests are indicated to rule out organic causes must be carried out. The mother and family must accept the non-organic nature of the disturbance. Some insight into the mother's personality and the occurrence of environmental frictions and tensions must be sought. The best advice to the mother concerns the ways and means by which clashes can be avoided, since her basic personality cannot be altered. If the underlying etiology can be determined, an attempt should be made to correct it. Some type of sedative, phenobarbital or a tranquillizer, should be prescribed in an attempt to afford both mother and baby some rest. A hypo-allergic feeding may be tried if the findings of mucus in the stool and an elevated eosinophil count suggest a diagnosis of milk allergy. The essential point in the management of this type of behaviour disorder is to try to prevent excessive crying by anticipating periods of friction between mother and child. When these do occur, an attempt should be made to diagnose the underlying cause in the environment and to treat the situation accordingly. Excessive crying is a symptom of some fault, not necessarily in the infant, but sometimes in the people about him and in their method of managing him.

Dr. N. T. Jaco, Chief of Pediatrics of Sudbury General and Sudbury Memorial Hospitals, defined his subject, "Concealed Infections", as those infections that are not found on examination of the infant, and that create problems in diagnosis. It is probable that most of these are not found because they are not looked for. The importance of a careful history and examination is obvious in this respect, and the more carefully these procedures are carried out, the less will be the number of so-called concealed infections. The development of a systematic routine method of careful examination is essential if obscure infections are not to be overlooked. The commonest of these are infections involving the ear, urinary tract, chest and meninges. Bone, joint and lymph node disease may also pose problems in the diagnosis of infectious processes in the infant. These lesions may be manifested in the form of septic arthritis, meningitis, mastoiditis, lung abscess, empyema, urinary infections or osteomyelitis, for example. Abdominal symptoms and signs may point to renal or intra-abdominal sites of infection but examination of the abdomen in the infant is difficult, and not uncommonly extra-abdominal lesions, for example, intrathoracic disease, may present with major symptoms and even signs referred to the abdomen. In the matter of management of these infections it must be remembered that fever alone is not an adequate indication for the use of antibiotics and that antibiotics are not antipyretics. If one is not sure of the diagnosis, antibiotic therapy should be withheld unless the child has an obviously severe or serious infection. The widespread use of antibiotics has introduced another category of concealed infection, that could be more properly termed "suppressed infection", a common and potentially serious problem. Empyema, subacute bacterial endocarditis, meningitis and osteomyelitis are some of the infectious processes that may be suppressed but not eradicated by inadequate antibiotic treatment.

Dr. J. Stobo Prichard, Assistant Professor of Pediatrics at the University of Toronto and Director of Electroencephalography, Toronto Hospital for Sick Children, in a presentation entitled "Intracerebral Lesions" pointed out that this group of disorders are usually associated with other evidences of intracerebral disease and that they rarely result in crying as the sole or presenting symptom. Such lesions include (1) Abnormalities of blood vessels; vasomotor disturbances such as migraine probably occur rarely if at all in the infant. (2) Meningeal irritation may be manifested by crying only, in the very young infant, but it is usually associated with other obvious signs. (3) Raised intracranial pressure is probably the most important of these three groups of lesions. In the very young infant, increased intracranial pressure does not usually result in pain or crying because the sutures and fontanelles allow the head to enlarge painlessly.

Another intriguing type of intracerebral disorder that may be manifested by crying in infancy is the poorly understood state that is commonly referred to by the term "the brain-injured child". In older children this is characterized by poor progress at school which is not due to any deficiency in intelligence. These children cannot concentrate for any length of time. In the infant this disorder may be manifested as hypertonicity. The control of the state of "tonicity" appears to be associated with the reticular substance of the thalamus. The disorder at this site may be of "functional" nature or it may be caused by an organic lesion. In the latter event, phenobarbital often seems to make the child worse. Reserpine is the treatment of choice in such cases.

Dr. D. L. A. Bastedo, Chief of Pediatrics at Kitchener-Waterloo Hospital, discussed the "Intra-Abdominal Conditions" that may be the cause of crying in infancy. These, he considered, usually fall into the following categories: (1) a small group in which the cause is an actual intestinal deformity, a specific intestinal infection, an acquired intestinal twisting or herniation, or urinary obstruction; and (2) a much larger group in which no specific structural change in the gastrointestinal tract can be demonstrated, but in which a pattern of incessant crying and abdominal discomfort necessitates a medical diagnosis which usually is expressed by the unsatisfactory terms "colic" or "indigestion".

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Specific structural lesions that cause an infant to cry are readily diagnosed by adequate examination of the undressed child, with the aid of laboratory and radiological procedures if indicated. It must be remembered that hernias in young children are frequently bilateral. Careful examination of the urethra and rectum are requisites of any conscientious investigation. The treatment of these diagnosable organic disorders is usually straightforward.

Diagnosis of non-structural causes of abdominal distress is usually reached after much trial-and-error empiricism. Their treatment, while most rewarding and necessary, is far from straightforward and indeed is often without scientific basis. Colic in infants, indigestion in toddlers, and abdominal pain in children is definitely on the increase. It is considered that the basic cause of this disturbed intestinal physiology is the increasing amount of emotional disorder in our changing family and social relationships. Such fear and anxiety as motivate and underlie the emotional disturbance might well be related to society's incessant drive for sundry amenities and frills.

The physician, to provide maximum assistance in quieting the intestinally disturbed infant, must be sympathetic to the total family unit. He must above all take time to listen to the parents and to make at least one visit to the home to adequately understand the mother's real problem. He must not take refuge in a defence mechanism of aloofness and criticism. Instead, the incessant cry of the intestinally disturbed infant should at once signal to him the need for a compassionate identification with this family and for an attitude of sympathetic understanding, a device far more valuable than the surgeon's scalpel or the apothecary's pill.

The chairman and contributors to the symposium then engaged in a panel discussion based largely on questions and comments submitted by their audience.

After a brief intermission, the session continued with the presentation of a report on the "Management of Common Types of Liver Disease" by Dr. J. C. Sinclair, Associate in Medicine and Bacteriology, the University of Toronto. Dr. Sinclair noted that *drug-induced hepatitis*, while not particularly common, is being encountered with increasing frequency. Liver damage produced by such hepatotoxic drugs as carbon tetrachloride and phosphorus has been familiar to all for many years. Drugs with a metabolic effect such as iproniazid (Marsilid) and pyrazinamide produce a very similar picture and are associated with a high mortality but a low incidence of liver involvement among persons exposed to these substances. Cholestatic drugs, which include chlorpromazine, norethandrolone (Nilevar), methyl testosterone, para-aminosalicylic acid, thiouracil and arsphenamine, result in a low mortality and a low incidence of liver damage in persons exposed to them. Their effect on the liver appears to be associated in some way with the phenomenon of hypersensitivity, and marked eosinophilia may be present during the early stages of liver damage by these drugs. A high alkaline phosphatase and serum cholesterol suggest the presence of obstructive jaundice in such cases. Liver damage may become evident within a week of administration of the cholestatic group of drugs and it may last for months. Fatalities are rare. As more experience is gained with the use of these drugs, it should become feasible to avoid that level of dosage at which cholestasis is encountered in a significant proportion of persons so treated. Because of the suggestive role of hypersensitivity in the hepatic reaction to the cholestatic drugs, treatment with corticosteroids appears rational.

Infectious hepatitis is by far the commonest form of liver disease in Canada. Close contact with infectious cases, especially in children, probably accounts for the majority of cases of orally acquired infectious hepatitis. It is now clear that infection due to the virus of infectious hepatitis has an intestinal phase, as does the virus of poliomyelitis. This accounts for the common occurrence of multiple cases in an infected family, a situation encountered with considerable frequency. Regarding measures designed to prevent spread of this infection, patients should be isolated for 10 days after development of jaundice and should be nursed with general sterile precautions and the usual sterile care of utensils, instruments and clothing. Gamma globulin may be used to prevent institutional spread by administering it to attendants, staff and others exposed to an infectious source. That gamma globulin provides protection from an attack was confirmed by Dr. Sinclair's experience in a comparatively recent outbreak at Elliot Lake, Ontario. The dose of gamma globulin advocated for this purpose is 0.02 c.c. per lb., intramuscularly. This measure is of no value after the onset of the illness. Pregnant women exposed to infectious hepatitis may require a somewhat larger dose of gamma globulin. There is no evidence, in Dr. Sinclair's experience, that infectious hepatitis during pregancy is associated with any increased incidence of congenital defects in the infants of such mothers. The nature of the protection afforded by gamma globulin is not fully understood. It is not simply a matter of providing passive immunity. Establishment of a precise diagnosis is of obvious importance. Difficulties in differentiation of infectious hepatitis from infectious mononucleosis, from hepatitis due to cholestatic drugs and other causes, and from extrahepatic biliary obstruction may at times be encountered. With regard to treatment, rest is an essential element, the strictness of which should depend on the severity of the illness. Alcohol should be avoided entirely for at least three months after recovery. If nausea and vomiting are sufficiently severe, intravenous glucose infusions may be required. A high carbohydrate, moderately high protein diet should be provided. If the hepatitis is severe and fulminating with progressive deterioration, 400 to 800 mg. of hydrocortisone should be administered intravenously, daily, if the patient is comatose; thereafter, or if the patient is not comatose, 150 to 250 mg. of prednisone should be given daily, with gradual reduction in the dose. Corticosteroids should be continued until liver function is normal. In addition, severe fulminating cases should receive 6 to 12 g. of neomycin daily in divided doses. Protein should be withheld until recovery is evident, at which stage it may be introduced at a level of 25 g. daily and gradually increased thereafter. Intravenous glucose infusions should be administered throughout the severe stage of the illness. In the presence of coma, arginine glutamate 150 to 200 g. daily, intravenously, for several days, may be of some value. Narcotics and short-acting barbiturates should be avoided.

Alcoholic cirrhosis in its early stages is manifested largely as a process of fatty accumulation throughout the liver with minimal fibrosis. This stage is capable of recovery if treated actively and if the patient adheres to the treatment regimen. Treatment consists of rest, a diet whose essential features are those of the average hospital diet with a carbohydrate content of 250 to

300 g., protein 75 to 100 g. and a moderate level of fat. Supplementary feedings by duodenal tube should be added if necessary. Lipotropic substances such as choline do not accelerate improvement if an adequate diet is consumed. Absolute abstinence from alcohol is a prerequisite to recovery. The prognosis in such cases is good if the patient adheres to this regimen and continues to abstain from alcohol. All available psychological and social facilities should be called into play to conquer the problem of alcoholism. In severe, advanced cases with edema and ascites, rigid control of sodium intake is essential if diuresis is to be induced. The majority of patients also require diuretics such as mercaptomerin or chlorothiazide. An adequate potassium intake must be ensured if chlorothiazide is used. In refractory cases spironolactone may induce diuresis in some instances when other diuretics fail to do so. Failing response to these measures, prednisone may be used. Paracentesis should be performed only if ascites is causing distress by the mechanical effect of a large collection of intra-abdominal fluid. Rest and dietary measures should be the same as those advocated for patients with fatty livers. If coma appears imminent, dietary protein should be restricted. The level of serum albumin is a valuable prognostic sign. If it remains low, the outlook is bad. If it begins to rise, the prognosis is reasonably optimistic. Hemorrhage from esophageal varices is one of the main causes of death in hepatic cirrhosis. If this complication occurs, the patient should be transfused and a Blakemore-Sengstaken tube should be inserted and left in place for 24 to 48 hours *under constant nursing supervision*. Following recovery the advisability of portacaval shunt surgery should be assessed. If the serum albumin exceeds 3 g. % and the serum bilirubin is less than 2 mg. %, the operative prognosis is reasonably good. If the reverse is the case, the outlook for survival of such an operation is poor. The patient's general physical condition, presence or absence of ascites, edema and jaundice, and state of prothrombin activity should all be considered in assessing the degree of risk in any case in which portacaval shunt is contemplated. There appears to be no indication for portacaval shunt on a purely prophylactic basis for patients with hepatic cirrhosis who have never had an esophageal hemorrhage.

The final paper, on the subject of "Tranquillizers and Antidepressant Drugs", was presented by Dr. Heinz E. Lehmann, Clinical Director and Associate Professor of Psychiatry, McGill University, and Visiting Associate Professor of Psychiatry, University of Cincinnati. Dr. Lehmann remarked that tranquillizers and antidepressant drugs, a fairly recent addition to the therapeutic armamentarium in medicine, can be categorized as psychotropic drugs, that is, agents with a direct influence on behaviour, perception, mood or thought processes. Alcohol, caffeine and certain narcotics are the oldest known pharmacological agents of this type. With the advent of scientific medicine, systematic research over the past 100 years led to the development of anesthetic and analgesic drugs and later to the introduction of a variety of hypnotic and sedative agents. It was only natural that the first remedies developed were those used for the universal ills of mankind, pain, insomnia and anxiety. Effective drugs for more specific uses in treatment of mental and emotional disorders have been systematically developed only in the last 10 years—to be exact, since 1952 when Delay and Deniker, in France, administered chlorpromazine for the first time to agitated psychotic patients and noted its extraordinary tranquillizing effect. The history of the newer drugs which have followed chlorpromazine, variously referred to as tranquillizers, neuroleptics, ataractics, energizers and antidepressants, can be divided into three phases. The first phase, that of impact, has been characterized by the surprised reaction of the medical profession to the utterly unexpected therapeutic effects of these drugs. The second phase, that of publicity, has been marked mainly by confusion when the general public, the press and big business were taken over by the tranquillizer boom. The third phase which we seem to be entering now is that of research which is gradually increasing the available amount of systematic and useful information. The need for rapid increase in research efforts in this field has led to the development of a new scientific discipline in the last decade. This new area of research, called psychopharmacology, is a complex interdisciplinary blend of pharmacology, psychology and psychiatry.

The psychotropic drugs may be categorized according to their relation to three basic parameters of psychological functioning: arousal, mental integration and mood. At the two extremes of the arousal parameter are stimulants and sedatives. Similarly related to the extremes of the parameter of mental integration are the psychotogenic and antipsychotic drugs. Regarding the parameter of mood, only one end of the scale is attacked by drugs available to date, namely the antidepressants.

The most commonly used stimulants are caffeine, the amphetamines, methylphenidate (Ritalin) and piperadol (Meratran).

Among the sedatives there are two main types, those producing diffuse and those producing selective inhibition of cerebral functions. Older sedatives such as the barbiturates and chloral hydrate have an approximately equal inhibiting effect on subcortical and cortical structures of the brain, while some of the newer tranquillizers, for instance the phenothiazines, affect the subcortical structures much more strongly than the cortex.

The three main psychotogenetic drugs are (1) mescaline, a substance derived from the Peyotl cactus; (2) LSD-25 (lysergic acid diethylamide), an ergotamine derivative; and (3) psilocybine, a substance obtained from a variety of Mexican mushrooms. These are currently used mainly for experimental purposes but they may possibly have some therapeutic role in the future.

There are four principal conditions for which the non-psychiatric physician most frequently requires pharmacological agents: anxiety states, depressions, acute psychotic breakdowns and chronic psychotic conditions requiring maintenance therapy. The use of drugs in these disorders is at best only symptomatic therapy. In anxiety states, barbiturates and minor tranquillizers such as meprobamate (Equanil), chloriazepoxide (Librium) and others in this category are more effective than so-called major tranquillizers such as the phenothiazines or reserpine, but they have a potential addiction hazard.

For depressed states, the antidepressant drugs available include monoamine oxidase inhibitors such as iproniazid (Marsilid), phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromide (Parnate) and etryptamine acetate (Monase). Antidepressants that do not inhibit monoamine oxidase include imipramine

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(Tofranil), amitriptyline (Elavil), and deanol (Deaner). It must be remembered that monoamine oxidase inhibitors have far-reaching metabolic effects that are not easily reversed and that constitute potentially dangerous reactions.

Among the antipsychotic agents, the prototype is chlorpromazine (Largactil), the first to be discovered and still used as the standard against which newer drugs are evaluated. The antipsychotic drugs may be roughly grouped as those with side effects manifested mainly by autonomic dysfunctions such as hypotension, miosis, dry mouth, excessive perspiration and other symptoms of adrenergic-cholinergic dysbalance; and those whose side effects are expressed mainly in the extrapyramidal system as parkinsonism or muscular dystonia. Drugs with a piperazine ring in their side chain are more potent and more likely to produce extrapyramidal symptoms than those with an aliphatic side chain, which are more likely to produce autonomic dysfunction and must be given in larger doses.

Phenothiazine derivatives with a dimethyl structure in their side chain include chlorpromazine (Largactil), triflupromazine (Vesprin), levomepromazine (Nozinan) and promazine (Sparine).

Phenothiazines with a piperazine ring in the side chain are prochlorperazine (Stemetil), perphenazine (Trilafon), thiopropazate (Dartal), trifluperazine (Stelazin), fluphenazine (Prolixin) and thioperazine (Majeptil).

Phenothiazine derivatives with a piperidine ring in the side chain include mepazine (Pacatal) and thioridazine (Mellaril).

Of this list, thioperazine produces extrapyramidal symptoms most often and thioridazine least often.

Almost any of the phenothiazine derivatives with antipsychotic properties will give equally good results in the hands of a physician who knows the proper indications, dosage and timing for their use.

Dr. Lehmann's exhaustive and far-ranging discussion included pertinent comments concerning the indications and contraindications, limitations, side effects and toxicity, and range of practical usefulness of this lengthy list of tranquillizing, antidepressant, energizing and antipsychotic agents.

SCIENTIFIC MEETINGS OF SECTIONS

In addition to the foregoing general sessions, scientific programs involving the presentation of a total of 44 individual papers and three panel discussions were held by the Sections of Anesthesia, Dermatology, General Practice, Geriatrics, Group Practice, Hematology, Internal Medicine, Neurology and Neurosurgery, Obstetrics and Gynecology, Orthopedic Surgery, Otolaryngology, Plastic Surgery, Psychiatry, Salaried Physicians, Surgery, and the Coroners Section.

MEETINGS OF ASSOCIATED ORGANIZATIONS

During the course of the annual meeting of the Ontario Medical Association, additional meetings were held by the Ontario Medical Secretaries' Association, the Ontario Chapter of the College of General Practice of Canada, the Federation of Medical Women of Ontario, and the Medical Directors of the Ontario Society for Crippled Children Treatment and Rehabilitation Centres.

EXHIBITS

The exhibit halls were filled to overflowing with the interesting and attractive displays of 92 commercial exhibitors, 17 medico-lay voluntary organizations and six scientific and clinical exhibits. D.C.G.

SEVENTEENTH ANNUAL MEETING, CANADIAN UROLOGICAL ASSOCIATION

The Seventeenth Annual Meeting of the Canadian Urological Association will be held in Montreal, at the Queen Elizabeth Hotel, on June 12, 13 and 14, 1961. The guest speakers include Dr. William Engel, Dr. B. A. Levitan, Dr. Hans Selye, Dr. Chester Stock and Dr. Willet F. Whitmore, Jr. The program is as follows:

Monday Morning, June 12

Symposium on Carcinoma of the Urinary Tract: (1) Recent Developments in Cancer Research, Dr. Chester Stock, New York; (2) Carcinoma of Testes and Treatment, Dr. G. D. Blue, Saskatoon; (3) Carcinoma of Prostate—Assessment and Treatment, Dr. Martin Spooner, Toronto; (4) Carcinoma of Kidney—Surgical Approach and Results of Treatment, Dr. Charles Robson, Toronto; (5) The Treatment of Bladder Tumour, Dr. Willet F. Whitmore, Jr., New York; (6) Endocrine Aspects of Tumour Therapy, Dr. William Engel, Cleveland, Ohio; (7) Chemotherapy of Tumours of the Urinary Tract, Dr. Willet F. Whitmore, Jr., New York. *12 Noon*: Film, Haemodialysis, Dr. Lionel Reese, London, Ont.

Tuesday Morning, June 13

Congenital Sponge Kidney, Dr. J. H. McBeath, Winnipeg; Partial Nephrectomy, Dr. Earl K. Vann, Winnipeg; The Retropubic Approach in Female Stress Incontinence, Dr. Gordon Mack, Halifax; Perineal Urethrotomy—Indications and a Method, Dr. James Metcalfe, Edmonton.

Symposium on Renal Hypertension: (1) Stress and Renal Disease, Dr. Hans Selye, Montreal; (2) The Assessment of a Patient with Renal Hypertension and the Medical Aspects of Treatment, Dr. B. A. Levitan, Montreal; (3) Asymmetry of the Kidneys in Bilateral Renal Artery Disease, Dr. Conway Don (by invitation), Ottawa; (4) The Surgical Treatment of Hypertension and the Newer Techniques of Increasing Blood Supply to the Kidney, Dr. William Engel, Cleveland, Ohio.

Wednesday Morning, June 14

CANADIAN ACADEMY OF UROLOGICAL SURGEONS

Report on Urinary Diversions by the Canadian Academy of Urological Surgeons: (1) Ileal Conduits, Dr. C. E. Jebson (by invitation), Halifax; (2) Ileocystoplasty and Ileoneocystoplasty, Dr. John Sales (by invitation), London; (3) Colocystoplasty, Dr. Z. Lewicki (by invitation), Montreal; (4) Sigmoid Bladder, Dr. William H. McCrae (by invitation), Toronto.

Experience with Bladder Reconstruction in Extrophy of the Bladder, Dr. Kenneth J. MacKinnon, Dr. Thomas N. Nearing and Dr. T. Lebetter (by invitation), Montreal; Extrophy of the Bladder with Hydroureters, Dr. Grant Reid and Dr. Murray McIntyre, Montreal; Renal Biopsy, Dr. Louis Coulonval, Quebec City; A New Technique for Orchiopexy, Dr. J. P. Bourque, Montreal.

GENERAL PRACTICE

REPORT OF THE COMMITTEE ON RESEARCH*

THIS committee is now in its third year of existence, and I am pleased to report very decided progress in the past twelve months.

Monthly meetings have been held in the Board Room at St. Joseph's Hospital, London, Ontario, during the past year, with the exception of the month of August. These meetings have been well attended, and a full agenda has been dealt with on each occasion.

Communication has been maintained, to a degree, with counterpart committees in the British Commonwealth, namely with those of Australia, New Zealand and Great Britain. Ultimately it is hoped to correlate some of our research projects and findings with those carried out in relatively distant areas of the globe, embracing widely varying climatic, topographic and population conditions as well as marked variations in the standards of living. Appended to this report is a list of suggested research projects. This list has been prepared as a guide for those who are interested, and although far from complete, contains quite a number of interesting subjects.

Our committee was greatly strengthened during this year by the addition of two consulting members, Dr. Harding LeRiche, Professor of Public Health, University of Toronto, and Dr. Carol Buck of London, Ontario. Dr. Buck is Associate Professor of Psychiatry and Preventive Medicine at the University of Western Ontario, and has considerable knowledge of, and interest in medical research. The addition of these two, and their attendance at our regular monthly meetings, has greatly expedited our work.

There follows a list of projects now under way, most of which have received financial support from our Central Committee.

1. *Phenylketonuria*

After careful consideration on the part of the committee, and at the suggestion of Dr. Michael Partington, of the Hospital for Sick Children, Toronto, it was decided to launch this project on a nation-wide basis, and under the direct sponsorship of the Central Committee. The test for this disease is so simple, its early recognition so important, and the recording of findings so completely free from difficulty, that the investigation seemed ready-made for us. Unfortunately, positive urinary findings do not appear until the end of three weeks or sometimes later, usually after discharge from hospital, so that this disease more than ever lends itself to office testing and recording, and falls directly within the scope of general practitioners and pediatricians. As a result, the total membership of the College of General Practice of Canada received through the mails, material for testing, a small booklet describing the disease, and a form for recording the findings. We hope in this way (1) to determine the incidence of the disease in our population, and (2) to pick up cases early enough for prompt and active treatment. It is well known that if the disease is not identified within the first two months of life the chance of successful treatment is very slim indeed.

An article was inserted in the *Canadian Medical Association Journal*, and a similar article in the *Bulletin of The College of General Practice*, describing the disease, and this apparently was read with a certain amount of interest because excerpts from this article appeared in several United States journals. So much so, that many requests have been received from both sides of the border for information concerning our project, for our booklets, and even for material for testing. As all our booklets had been used with the first mailing, it was decided to order another supply in order that we might have some to meet the numerous requests that are coming in.

2. *Measles Project*

The measles project is being handled by a group of general practitioners and pediatricians in London, Ontario, and its immediate vicinity. I was surprised, on discussing measles with a number of physicians in our area, to find that there was a marked difference of opinion as to the advisability of treating the disease with prophylactic antibiotics. Most believe, particularly pediatricians, that antibiotics should be used only if and when complications arise or, rarely, prophylactically in the case of the severely debilitated child, or one who for one reason or another would probably not stand complications well. A definite minority group believe that antibiotics should be given in every case, thereby (so they contend) averting every possibility of the development of complications. This in spite of the fact that, to my knowledge, it has never been definitely proved that the use of antibiotics has prevented complications.

We are conducting a double-blind study under the direction of Dr. Keith Johnson of London, Ontario, to attempt to show whether or not the use of antibiotics has any effect on the development of the common complications of red measles. The drug used in this case is Penvee S., supplied through the courtesy of John Wyeth & Co. at no charge to the investigating group. With the help of Dr. Buck, a card was drawn up for the statistical interpretation of this study. On this card are marked various data such as the date of first symptoms, the date the rash appeared and the date that medication was started, etc. A copy of the card is available on request. To the present date, this study has been rather hampered by the fact that the expected outbreak of red measles in the London area has not developed.

*Presented at the National Scientific Assembly, The College of General Practice of Canada, Vancouver, March 1961.

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3. *Histoplasmin*

Dr. E. L. Brown of St. Thomas, Ontario, has for several years been interested in histoplasmosis, which for some reason has been particularly prevalent in his area. Dr. Brown has skin-tested over 4000 people in St. Thomas and its immediate vicinity, during the past two or three years, and has carried out extensive soil testing in an attempt to determine the reason for the high incidence of this relatively uncommon disease entity in that particular area. Dr. Brown is on the scientific program of this meeting, and I am sure that you will be interested in his theories and findings. He has received financial assistance and co-operation from our committee to the fullest extent required.

4. *Tuberculin Skin-Testing Program*

In the metropolitan Toronto area, seven general practitioners have agreed to carry out tuberculin skin-testing on all patients who are seen in their respective offices during an unstated length of time. The object of this project is, fundamentally, to determine whether or not blanket tuberculin testing in a general practitioner's office is a worthwhile and feasible procedure. This project has been approved by our committee and is being directed at the present time by our Secretary, Dr. Reg. Anderson. This should probably be classed as a pilot study.

5. *Study of Blood Cholesterol Levels in Children and Young Adults*

This interesting study is about to be undertaken by a group of College members of the English Metropolitan Montreal Chapter. It is under the leadership of Dr. A. B. Mayman, Chairman of the Research Committee, and Dr. I. A. Schlesinger, President of the Chapter. This study, which has been carefully thought out, is an attempt to determine whether the blood cholesterol levels in children and young adults are higher in families that have a known history of coronary artery disease, early arteriosclerosis, etc., and also to determine at what age elevated blood cholesterol levels are likely to be found if they do occur. Financial support of this project has been promised by the committee.

6. *Diabetes Research*

The project on diabetic research has been contemplated by Dr. J. A. Ballard of Rosetown, Saskatchewan. A remarkable increase in the number of diabetics has been discovered in that area, and this has sparked interest in this particular field of research. The exact nature of this project has not as yet been determined, but it is receiving direction, according to my information, from Dr. I. M. Hilliard, Professor of Medicine at the University of Saskatchewan. Doubtless we will have something concrete to report from this group at our next meeting.

7. *Psychiatric Workshop*

A psychiatric workshop was conducted by Dr. D. G. McKerracher, Professor of Psychiatry, University of Saskatchewan, Saskatoon, early in 1960.

A letter was directed to Dr. McKerracher in February of this year, but at the date of this report, no reply had been received. It is my belief, however, that the Workshop was very successful and beneficial. This project received financial sponsorship from our committee.

A considerable number of the other projects, and applications for funds to carry them on, have come to our attention. Some of these have been deferred, some rejected as impractical for one reason or another; others have come to our attention so recently that we have not been able to compile enough information to finalize them. Further consideration will be given to these when more details are available. Among this latter group, the following are worthy of note.

1. Dr. G. A. Pengelly of Willowdale, Ontario, is contemplating research on the values of preprandial and postprandial blood sugar levels with relation to the clinical assessment of diabetic control.
2. Dr. H. F. Dyer of Hamilton, Ontario, is conducting special studies on gastric acidity.

On the whole, the Central Committee of Research for the College of General Practice of Canada is happy with the turn of events during the past 12 months. We are just arriving at the point where general practitioners are becoming interested in clinical research, and it is, I believe, a healthy sign when groups begin writing in for direction and assistance with projects which they have originated. Previously, we had the unhappy feeling that new projects were going to have to originate from the Central Committee.

I would like to point out that the financial status of our committee is still excellent, owing to the annual renewal of our grant from Mead Johnson and Company.

If you have a research project in mind, we would be more than pleased to hear from you, and to render help in any manner possible, whether advisory or in any other capacity. If we feel that your aims are carefully considered, and that the need is clearly shown, financial aid will, of course, be forthcoming.

I am convinced that any success that this committee may have experienced in the past year is largely due to the indefatigable efforts and the enthusiasm of our Secretary, Dr. Reg. Anderson, and to all the members of our committee, both active and advisory, for their ready and willing help. I would also like to express my appreciation to St. Joseph's Hospital of London, Ontario, whose Board have been very co-operative with our Committee in every respect.

All of which is respectfully submitted.

Chairman	Dr. W. R. Fraser
Secretary	Dr. R. M. Anderson
Treasurer	Dr. G. Hamilton
Members	Dr. H. G. Fletcher Dr. F. F. Boyes Dr. E. Jeffrey
Advisory	Dr. H. leRiche Dr. Carol Buck

SUGGESTED RESEARCH PROJECTS

1. Studies of epilepsy—with special emphasis on incidence, family history and results of treatment.
2. Studies of the consequences of febrile illnesses in pregnancy. A comparative study of the status of children from control pregnancies and pregnancies complicated by a febrile illness. Laboratory diagnosis of the febrile illness might be considered if reasonably simple methods could be used.
3. Studies of the consequences of vaginal bleeding during the first 28 weeks of pregnancy:
   —frequency of abortion;
   —condition of infant at birth.
4. Controlled studies of the use of triparanol (MER/29) in the prevention of vascular complications of early diabetes and in the prevention of atherosclerosis.
5. Further studies of the incidence of histoplasmosis.
6. Controlled clinical trials of antibiotic prophylaxis of the complications of measles. One such trial is now in operation in the London, Ontario, area.
7. Studies of the frequency of congenital malformations among infants born to mothers exposed to but not attacked by rubella in pregnancy, comparing the outcome in those whose mothers had had rubella in childhood with those who had not. Such a study would require the participation of many physicians in order to obtain sufficient numbers of relevant cases.
8. Studies of diabetes—with special emphasis on such aspects as:
   —family history;
   —status of infants born to diabetic fathers;
   —dietary history.
9. Studies of rheumatic fever after streptococcal infection. A study of children afflicted with streptococcal infection (all with laboratory diagnosis), comparing those who do develop rheumatic fever with those who do not in terms of the many factors which have been suggested as possibly influencing susceptibility to the rheumatic response.
10. Studies of the incidence of serious automobile accidents among patients with diseases or defects that are alleged to increase the risk of such accidents.

W. R. FRASER, London, Ont.
Chairman, Committee on Research,
College of General Practice of Canada

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

REGULATIONS RELATING TO THE TRAINING REQUIREMENTS IN PSYCHIATRY

The period of training and study in psychiatry required for eligibility for either the Fellowship or Certification examinations of the College should be organized under university auspices to achieve an overall psychiatric experience. This training involves a minimum of four years of approved training after the general internship.

Two of the years of advanced training must be spent with the resident involved in an intensive teaching experience in an organized training program of a university department of psychiatry. During these two years there should be experience on the psychiatric service of a general hospital, experience in an outpatient clinic dealing with community psychiatric problems, experience in child guidance in psychosomatic medicine and on a neurological service and in other settings approved by the university to meet special needs. There should also be contact with other medical disciplines and with the basic specialties in psychiatry.

The additional two years of advanced training provide a wider choice for the trainee. However, these two years of training must include at least six months and preferably one year in a hospital providing an opportunity for the study of the comprehensive care of psychotic patients for a sufficiently long period to permit the resident to observe the natural course of the illness and its treatment. During such time the resident would be receiving training in methods of therapy and gaining some experience in the medicolegal problems peculiar to this type of institution.

TRAINING REQUIREMENTS FOR FELLOWSHIP EXAMINATION IN MEDICINE MODIFIED FOR PSYCHIATRY AND CERTIFICATION EXAMINATION IN PSYCHIATRY

1. An approved general internship of at least one year.

2. Four years of graduate training in addition to the general internship. This period must include:

(a) Two years of approved resident training in psychiatry during which the trainee participates in the organized training program of a university department of psychiatry (read preamble carefully). (b) Two further years of approved training which may include (read preamble carefully): (i) One or more years of resident training in psychiatry in an approved mental hospital. (ii) One or more years of further approved training as outlined under section 2(a), provided such training includes the necessary minimum experience in the treatment of psychotic patients. (iii) One year of approved resident training in internal medicine. (iv) One year in the full-time study of related basic science such as neuroanatomy, neurophysiology, psychology or sociology in a department approved by the College. (v) Six months of approved full-time study of a related basic science and six months of approved resident training in internal medicine, pediatrics or other branch of medical practice related to psychiatry. (vi) One year in an approved course of study and training at a hospital or university centre in Canada or abroad. (vii) One year in a psychiatric specialty such as child psychiatry, community psychiatry or research.

January 1961

ONLY NINE MORE DAYS UNTIL...

THE 94th ANNUAL MEETING OF THE CANADIAN MEDICAL ASSOCIATION MONTREAL – JUNE 19 - 23, 1961

Aerial view of Montreal

OUR HOST CITY

As it is anticipated that 2000 Canadian doctors and their wives will visit Montreal during the week of June 19, the above photographic guide should assist in pinpointing hotels and other places of interest. Simply check the corresponding numbers, listed below, with those in the photograph—and the task of finding your way in this colourful city will be made a little easier:

1. Dominion Square
2. Canadian Pacific R.R. Terminal
3. Laurentien Hotel
4. Bus Terminal
5. La Salle Hotel
6. Windsor Hotel
7. Sheraton Mt. Royal Hotel
8. Mary Queen of the World Cathedral
9. Queen Elizabeth Hotel
10. Canadian National R.R. Terminal
11. Airline Terminal
12. McGill University Campus
13. Palais du Commerce

BIENVENUE À MONTRÉAL

ASSOCIATION NOTES

LE 94e CONGRES ANNUEL: PROTOCOLES DE CAS A DISCUTER A LA CONFERENCE CLINICO-PATHOLOGIQUE, LE 22 JUIN

Deux sommaires de cas reproduits ci-dessous seront les sujets de discussion à une conférence clinico-pathologique qui aura lieu le jeudi 22 Juin, durant le Congrès annuel de l'Association. Le Dr Douglas G. Cameron, Montréal, sera le Président de la conférence et les autres participants seront: Dr Gardner C. McMillan, Montréal, et Dr Carlton Auger, Ville de Québec, pathologistes; Dr C. C. Gray, Toronto, Dr R. C. Dickson, Halifax, Dr John Kilgour, Winnipeg, et Dr John Howlett, Montréal, cliniciens.

Les membres de l'Association qui désirent assister au Congrès annuel sont invités à étudier ces protocoles à loisir à la maison, afin de pourvoir leur discussion d'intérêt supplémentaire à la conférence clinico-pathologique et afin de recueillir le maximum de profit instructif de cette session.

Cas 1

En 1954, une femme âgée de 63 ans accusait de la dyspnée d'effort et une vague douleur précordiale; en 1956, elle faisait de l'œdème aux jambes. En juin 1956, on nota la présence d'un épanchement pleural droit et on pratiqua une thoracentèse. Elle manquait d'appétit et avait déjà perdu beaucoup de poids et d'énergie; elle était pâle. L'œdème des jambes répondit relativement bien à un traitement à domicile. Elle avait constaté dernièrement que le moindre traumatisme laissait des marques.

Première Hospitalisation

Le 8 octobre 1956, elle fut hospitalisée à l'hôpital Royal Victoria pour des symptômes qui duraient depuis 4 jours: nausées, vomissements, diarrhée, faiblesse, étourdissements et sensations de brûlure à la miction. Ses antécédents révélèrent qu'elle subit une amputation du pied gauche à 12 ans, à la suite d'une blessure; qu'à 16 ans, elle fut opérée pour une perforation de l'appendice et à 31 ans pour une hernie; elle eut 4 grossesses normales, mais d'autre part fut toujours bien portante jusqu'au début de la maladie actuelle. Ses parents étaient morts, l'un à 56 ans, l'autre à 65 ans, tous deux d'affection coronairienne. La même maladie avait aussi emporté son mari en 1950.

A l'examen, on nota des signes d'amaigrissement, mais la malade ne semblait pas souffrante. Sa température était normale; le pouls à 90 et la tension artérielle à 135/105 (subséquemment 110/70). Elle pesait alors 123 lb. Les fundi, ne montraient rien que ne pouvait expliquer son âge. On constata que le lobe thyroïdien droit était hypertrophié, mais lisse et non douloureux. On observa une matité et une diminution des bruits respiratoires à la base du poumon droit, un faible souffle systolique apexien et une sensibilité, à la pression, au point costo-vertébral droit et au quadrant supérieur droit. Il existait aussi une amputation transtarsienne gauche, mais rien d'autre d'important.

La densité urinaire était de 1.022; pas d'albumine; globules rouges: 20-30 et globules blancs: 10-15 par champ (fort grossissement). A la culture on obtint une croissance moyenne d'*Alcaligène fécal*. La cystoscopie révèla une muqueuse vésicale enflammée, une urine claire des deux uretères, des pyélogrammes normaux et la possibilité d'une pression externe sur l'uretère droit. L'hémoglobine était à 96%; l'hématocrite à 45 et la vitesse de sédimentation à 11. La numération des globules blancs s'élevait de 10,200 avec une légère neutrophilie. Les facteurs de coagulation étaient normaux. La radiographie et la fluoroscopie pulmonaires montrèrent la présence d'ombres, aux parties inférieures des deux espaces pleuraux, compatibles avec des épanchements ou épaisissements pleuraux, moyen à droite et léger à gauche, cachant les pourtours du cœur dont on ne put facilement déterminer le volume. Le lavement baryté ne montra rien d'anormal.

Elle reçut de la digitale, de la Dramamine (contre les nausées), du sulfisoxazole, puis du Furadantin pour l'infection urinaire. On observa que la vessie avait saigné excessivement après la cystoscopie si bien que même à la date de son congé elle faisait encore de l'hématurie microscopique.

Deuxième Hospitalisation

Le 30 octobre 1956, la malade revint à l'hôpital car le lendemain de son départ elle avait passé des urines rouges et des caillots; elle vomissait aussi depuis 24 heures. Son teint était fiévreux et elle semblait égrotante; cependant sa température était normale. Les symptômes étaient les mêmes que lors de son hospitalisation précédente, sauf que ses yeux étaient quelque peu exorbités et donnaient à son regard une certaine fixité. La tension artérielle était à 90/60 et le foie, lisse et légèrement sensible, était palpable à un travers de doigt au-dessous du rebord costal droit. Le toucher vaginal et la cytologie cervicale furent négatifs. La densité de l'urine était à 1.023 avec 1 + d'albumine, de nombreux globules rouges, quelques globules blancs, mais absence de cylindres. L'hémoglobine se chiffrait à 86%; l'hématocrite à 41; la vitesse de sédimentation à 21 et la numération globulaire (blancs) à 5,400. Les plaquettes ainsi que les temps de saignement, de coagulation et de prothrombine étaient normaux. La moelle osseuse montrait une hyperplasie généralisée compatible avec la récente déperdition sanguine. La malade passa trois fois à la cystoscopie à cause des hémorragies répétées de la vessie. Au

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cours d'un de ces examens, 2 régions ulcérées sur la paroi postérieure furent coagulées. Une biopsie ramena du tissu inflammatoire. La troisième cystoscopie montra plusieurs foyers sous-muqueux d'hémorragie que l'on interpréta comme manifestations de cystite interstitielle. La pyélographie ascendante fut normale. La culture des urines produisit des coliformes et des streptocoques anaérobies. Le traitement comprit des sulfamides, du Furadantin, de la tétracycline et de l'oléandomycine. L'hématurie macroscopique disparut en moins de trois semaines, mais l'hématurie microscopique était encore présente lorsque la malade quitta l'hôpital, le 2 décembre 1956. Sa tension artérielle s'était maintenue à un niveau moyen de 120/70 et son poids avait baissé de 121 à 115 lb.

TROISIÈME HOSPITALISATION

Elle fut de nouveau hospitalisée le 2 mars 1957 pour traitement d'un œdème périphérique et de dyspnée qui s'étaient réinstallés de façon progressive et ne répondaient plus à la digitale, aux mercuriels, ou au Diamox. La malade devait prendre deux oreillers pour dormir; elle avait gagné 30 lb. et pesait alors 145 lb. Elle était dyspnéique même au repos. Son corps était parsemé d'ecchymoses et elle avait une hémorragie à la sclérotique droite. La tension artérielle était à 140/90 et le pouls à 70 comprenait un grand nombre d'extra-systoles. Les deux lobes de la glande thyroïde étaient durs et formaient le siège d'une hypertrophie nodulaire. Il y avait des râles humides à base des deux poumons et une matité à la base droite. Un gros œdème s'étendait à la paroi abdominale inférieure, au sacrum et aux jambes.

L'analyse d'urine, sauf une trace d'albumine, était négative. L'azote non-protéinique du sang (N.P.N.) était à 31 mg. pour 100 ml.; les protéines totales à 5.32 grammes pour 100 ml. l'albumine, à 4.15 les globulines, à 1.17; le cholestérol à 200; l'iodémie protidique (P.B.I.) à 6.5 et la captation de l'I^{131} de 10.2% en 24 heures. Lors de son entrée à l'hôpital, le bilan des électrolytes montrait une baisse du chlore, qui se corrigea par la suite pour atteindre la normale; le sodium et le potassium furent trouvés normaux au cours de trois déterminations.

QUATRIÈME HOSPITALISATION

La malade revint à l'hôpital le 29 septembre 1957. Elle s'était portée relativement bien jusqu'en juillet 1957, lorsque réapparut l'œdème des jambes sur lequel la digitale et les diurétiques n'avaient plus exercé aucun effet. Elle avait gagné 13 lb. de poids et se plaignait d'œdème des jambes, d'anorexie, de somnolence, de nycturie (x2); de besoins impérieux et de saignements et de bleus aux moindres coups. Elle était apyrétique et semblait amaigrie malgré l'œdème prononcé de ses jambes. Les deux lobes thyroïdiens étaient rénitents et fortement augmentés de volume. La tension artérielle se tenait vers 115/80 et le pouls à 96 était régulier. Il y avait matité et diminution des bruits respiratoires à la base droite et distension des veines jugulaires externes, plus prononcée à droite qu'à gauche. Le foie était palpable à trois travers de doigts sous le rebord costal droit. La paroi thoracique antérieure portait de nombreuses ecchymoses et la région sacrée montrait une décoloration brunâtre. Le signe du lacet était positif.

La densité de l'urine était à 1.010 avec 2 + d'albumine; les leucocytes variaient de quelques uns à plusieurs par champ; les globules rouges de 0-24; on notait aussi la présence de cylindres granuleux. La culture des urines montra du *E. coli Communior* et des streptocoques. L'hémoglobine était 99%; l'hémotocrite à 51; la vitesse de sédimentation à 13; la numération des globules blancs à 8,800 et le différentiel normal. Les plaquettes sanguines, ainsi que les temps de saignement, de coagulation et de prothrombine étaient normaux. L'électrophérèse indiqua une hausse de l'alpha-2 globuline. Les chlorures se chiffraient à 94 mEq. au litre, le sodium à 134 et le potassium à 6.2. Une radiographie pulmonaire en date du 2 octobre révéla une hypertrophie cardiaque, difficile à préciser, une congestion pulmonaire modérée et un épanchement pleural droit. L'électrocardiogramme montra la présence d'un rythme sinusal, un temps de conduction normal, une absence d'ondes Q et des ondes R dentelées en V5 et V6 indiquant un bloc de branche gauche et des complexes ST-T de type digitalique en AVF, dérivations 3, V5 et V6. On poursuivit le traitement avec une diète hyposodée, de la digitale et, occasionnellement, des injections de mercuriels. On constata alors une amélioration temporaire suivie d'une augmentation pondérale progressive. Les manifestations hémorragiques persistèrent, de même que les régions ecchymotiques et les hématomes aux points de pression et à la suite de petits traumatismes, mais on n'observa pas de pétéchies ou de purpura. Une hématurie macroscopique, notée dix jours après l'admission à l'hôpital, disparut spontanément dans l'espace de 4 jours. L'administration de chlorothiazide ne produisit aucun effet sur l'œdème. Le 8 novembre, on entreprit un traitement à la prednisone, qui permit une faible diurèse au début. Le 11 novembre, la malade vomit plusieurs fois et accusa une forme de xanthopsie manifestée par des stries jaunes dans son champ visuel. Le même soir, elle ressentit une forte douleur épigastrique et se plaignit de dyspnée. On constata qu'elle avait "mauvais teint". Le 12 novembre, la dyspnée s'accentua et on perçut plusieurs râles aux bases. Le pouls se tenait à 84, s'accompagnant parfois d'extra-systoles; la tension artérielle était à 110/60. La malade devint très angoissée, mais elle passa une bonne nuit. Le 13 novembre, à 6 h. 30 du matin, elle demanda la bassine. Quelques instants plus tard, on la trouva morte dans son lit.

CAS 2

A LA SUITE d'un traumatisme survenu en octobre 1960, un homme de 64 ans, de race blanche, constata un jour une éruption à la jambe gauche. Ce rash ne disparut jamais complètement et trois mois plus tard il s'étendit au tronc et aux autres membres.

PREMIÈRE HOSPITALISATION

Le 4 janvier 1961, le patient fut admis à l'hôpital, se plaignant d'une éruption prurigineuse. Le seul antécédent de quelque importance remontait à trois ans auparavant. Il avait alors souffert de goutte aux gros orteils et ensuite au genou gauche. Durant deux ans on le traita exclusivement à la colchicine et, la troisième année, on ajouta de la Butazolidine au traitement. On arrêta cette double médication trois semaines avant l'entrée du patient à l'hôpital. Sa mère était morte d'asthme à 56 ans et son père, de cancer à 71 ans. Un frère avait succombé à l'hypertension artérielle.

L'examen d'admission donna: T. 99.4°, P. 70, T.A. 150/95. On nota alors que l'éruption s'étendait à tous les membres et à l'avant du tronc. Elle était maculo-papuleuse, confluente et sèche. Les poumons étaient nets et le cœur normal. Le poids habituel de 195 lb. n'avait pas changé. Les articulations n'étaient pas difformes mais il y avait un très léger œdème pré-tibial. La densité urinaire s'élevait à 1.017 et un échantillon, prélevé du patient à l'état fébrile, contenait des traces de protéine et 5-8 globules rouges. L'azotémie uréique était à 21 mg %. Des bains d'amidon et des compresses d'eau et de lait eurent lentement raison de la dermatite. Le troisième jour d'hospitalisation, une crise aiguë de goutte se manifesta au gros orteil droit. L'ACTH et le Bénémide en eurent bientôt raison. On prescrivit ensuite des doses d'entretion de colchicine et de Bénémide et, le 21 janvier, le patient retournait chez lui libre de tout symptôme.

DEUXIÈME HOSPITALISATION

Le 22 février 1961, le patient fut réadmis à l'hôpital, souffrant de dyspnée aiguë, d'œdème et d'oligurie. Il était demeuré bien portant jusqu'à deux semaines avant sa réadmission. A ce moment, il avait été atteint d'un mal de gorge et d'une toux accompagnée de légères expectorations parfois striées de sang. L'urine qui avait diminué en volume était colorée brun-thé. On notait de l'anorexie et une diarrhée légère. On discontinua alors la colchicine et le Bénémide. Dix jours avant la réadmission à hôpital, le patient accusa de l'œdème, des bouffissures des paupières et des maux de tête. Il fut admis en grande dyspnée; son poids avait augmenté de 15 lb.

L'examen donna: T. 100°, P. 108, R. 28, T.A. 130/80. Le malade était dyspnéique mais sans cyanose. Tout le pharynx était injecté de sang, le pouls régulier, le cœur de grosseur normale, les sons cardiaques nets, mais on pouvait distinguer un rythme de galop. On percevait de la matité aux deux bases et on entendait des râles humides aux deux plages pulmonaires. On remarqua de l'œdème à godet aux chevilles mais aucune turgidité des veines jugulaires. Le teint était clair. On nota de la torpeur, un langage léthargique et des mouvements convulsifs des extrémités. L'urine passée à ce stage était fortement colorée et titrait à 300 mg % de protéine. On n'en fit pas d'examen microscopique. L'azote non protéinique du sang se chiffrait à 70 mg %. Le tableau clinique de l'urémie étant devenu évident, on transféra le malade au Montreal General Hospital le 25 février 1961.

TROISIÈME HOSPITALISATION

L'état du malade à son arrivée dans cette institution était sensiblement le même: T. 99.6°, P. 100, R. 26, T.A. 150/85, Poids 203 lb. Il n'y avait pas d'hémorragie de la rétine, ni d'œdème des papilles mais on pouvait voir un exsudat rétinien. On nota des râles humides aux bases et des signes d'épanchement pleural bilatéral. La matité des flancs se déplaçait dans le décubitus latéral. L'urine prélevée à l'admission (quantité insuffisante pour en déterminer la densité) était de couleur café et contenait 300 mg % de protéine, une quantité considérable de globules rouges, de même que des cylindres hyalins, granuleux et d'hématies. A l'admission, le laboratoire rapporta une azotémie à 69 mg %, 89 mEq/L de chlorures, 21 mEq/L de bicarbonate, 118 mEq/L de sodium et 6.7 mEq/L de potassium. L'hémogramme donna les résultats suivants: Hgb. 10.7 gm., hématocrite 33%, taux de sédimentation 33 mm., réticulocytes 1%, globules blancs 12,100 avec 86% de polynucléaires, 4% de lymphos et 6% de monos. Un électrocardiogramme montra une tachycardie sinusale. Le radiographie pulmonaire révéla de légers épanchements bilatéraux de la plèvre, de la congestion pulmonaire et une ombre cardiaque dans les limites de la normale. Un film simple de l'abdomen laissa voir un contour normal des reins et aucune opacité suggérant la présence de calculs.

Un cathéter fut introduit dans la veine cave inférieure; l'ingestion de liquide fut réduite à 400 cc. par jour, plus une quantité équivalente à la production quotidienne d'urine. Chaque jour on enregistra le poids. Le patient fut digitalisé; on lui administra des résines échangeuses d'ions et des hormones anaboliques. Pendant les huit premiers jours, la quantité d'urine varia de 50 à 300 cc. par 24 heures. Le poids baissa à 194 lb., la torpeur se dissipa sensiblement et les convulsions musculaires diminuèrent. Le niveau du potasium descendit à 4.7 mEq/L mais l'azotémie atteignit 150 mg %. Le patient avait des nausées, sans vomissements, et il n'était pas incommodé par la diarrhée.

L'examen bactériologique de la gorge produisit une forte culture de staphylocoques pyogènes. Le cinquième jour de l'hospitalisation, on pratiqua une biopsie rénale dont on obtint des cultures stériles. L'antistreptolysine "O" titra à 168 unités

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par cc. L'urine passée au sixième jour contenait 33 mEq/L de sodium, 44 mEq/L de potassium et montrait un index osmotique de 352 m.osm./L. Des analyses microscopiques répétées de l'urine donnèrent les mêmes résultats qu'aux examens antérieurs.

Durant les six derniers jours de son existence le patient demeura oligurique (production urinaire par 24 heures: 0-200 cc.) et son état général demeura tel quel. Grâce à une administration sévèrement contrôlée des liquides et des électrolytes, son poids diminua de une à deux lb. par jour. Le 11 mars apparut une diarrhée liquide; le patient devint somnolent. Le même jour, l'analyse chimique du sang indiqua une azotémie à 198 mg %, 21 mEq/L de bicarbonate et 4.4 mEq/L de potassium. On résolut de procéder à une épuration extra-rénale par dialyse dès le lendemain matin.

Mais, dans la même nuit, après avoir traversé des périodes d'agitation et d'hypotension, le patient suffoqua et mourut soudainement aux petites heures du 12 mars.

LADIES' PROGRAM

ARE YOU KEEN ON GOLF?

If you are, be sure to bring your clubs and golf togs with you when you come to Montreal for the Annual Meeting of the Canadian Medical Association, June 19-23. A tournament for the ladies has been arranged for Thursday, June 22, at the Mount Bruno Golf Club. This beautiful course is situated at the foot of Mount Bruno on the south shore of the St. Lawrence River. All those who wish to take part will meet at the Queen Elizabeth Hotel, and transportation has been arranged from the hotel to the club. An informal buffet lunch will be served in the clubhouse. The John Eaton Trophy will be given for low gross on eighteen holes and there will also be other prizes for the non-experts. Mrs. C. Miller Ballem and Mrs. Gaetan Jarry, who are in charge of the arrangements, hope that many of our visitors will spend the day golfing with us and also hope that everyone saw the notice in the *Canadian Medical Association Journal* of May 27 (p. 1213).

SHOPPING

Mrs. Gordon Young and Mrs. Jacques Bruneau, Co-chairmen of Shopping, and their committee will be available during the three days of the meeting to help you with your shopping. Montreal has become noted as a world shopping centre, and specialty shops of every kind flourish in the city. Exquisite articles from France, England, Italy, other European countries and the Orient can be found here as well as the many interesting and artistic ceramics, carvings, paintings and woven goods from the Province of Quebec. The committee has prepared a brochure listing stores and boutiques of all kinds, as well as restaurants where you may wish to dine, and this will be given to you at registration. The committee will be happy to help you find what you want.

Posen

Mrs. C. Miller Ballem (left), Co-chairman with Mrs. Gaetan Jarry, of Golf, and Mrs. Gordon Young (right), Co-chairman with Mrs. Jacques Bruneau, of Shopping, make plans for visitors at the 94th Annual Meeting of the Canadian Medical Association.

If your children are coming with you and you would like them looked after while you go to luncheon, the wine-tasting party, or the Mayor's reception, Mrs. James Darragh and Mrs. Bernard H. Doray will arrange baby sitters to take care of them.

The weather if seasonable should be warm, or even hot in the 80s or 90s, and probably humid. However, as Montreal climate is variable, it is wise to bring a light coat or wrap. Don't forget to pack your party dress. For the banquet and dance either short or long evening dress, whichever you prefer, may be worn.

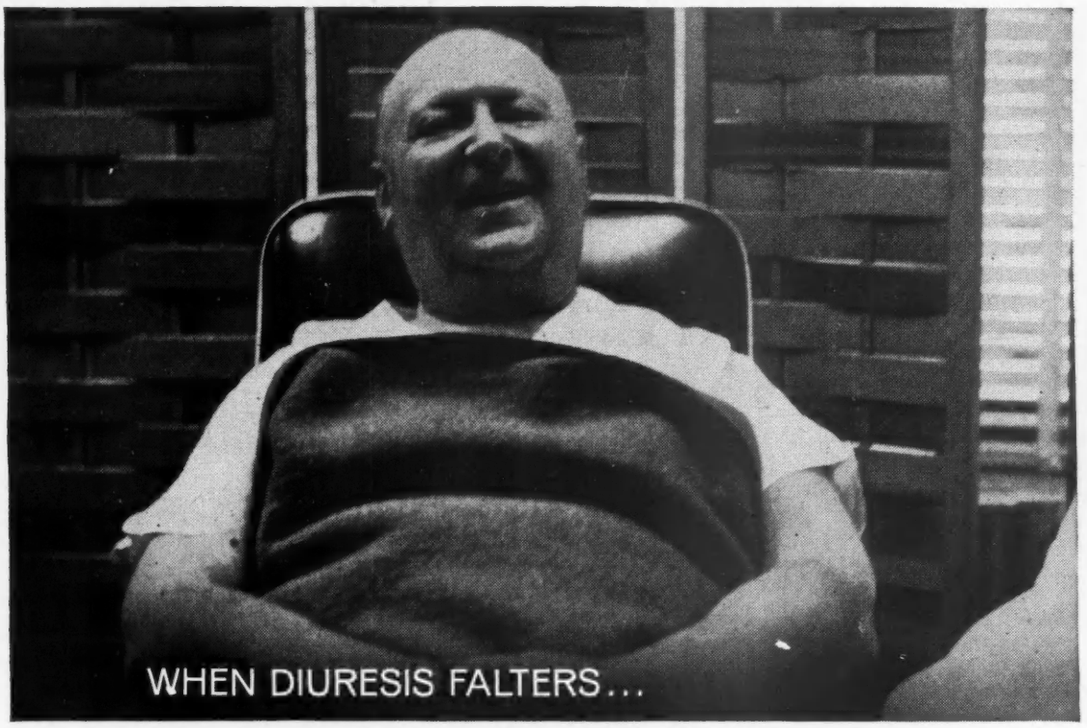
We are looking forward to welcoming you to Montreal in June. MARY WEIL

WINE-TASTING PARTY

On Monday evening, June 19, delegates and their wives will have the opportunity of participating in a unique and colourful event—a wine-tasting party, arranged by the Quebec Division of the C.M.A. The number of tickets will be limited to approximately 400. The party will be held from 6.30 to 8.30 p.m. in the Montreal Museum of Fine Arts, 1379 Sherbrooke Street West. Apart from sampling some 12 different imported wines, you will enjoy tasty cheeses, hors d'oeuvres and pastries.

CIVIC RECEPTION

An interesting and colourful event on the social program will take place on Thursday evening, June 22, when the City of Montreal will give a Civic Reception to all those attending the meeting. The Reception will be held at The Chalet on Mount Royal, commencing at 6.00 p.m. Buses will leave the Mansfield Avenue entrance of the Queen Elizabeth Hotel at 5.45 p.m.



ALDACTAZIDE

Brand of spironolactone (Aldactone®) with hydrochlorothiazide

When resistance to conventional diuretic management develops, Aldactazide offers the only preparation that gives positive diuretic activity in *both* proximal and distal convoluted tubules of the kidneys. This matched activity provides true synergistic diuretic effects in relief of edema and ascites, thus promoting much greater response than can be obtained with either drug alone.

Hydrochlorothiazide provides a vigorous diuretic action which is principally confined to the *proximal* convoluted segment of the renal tubules. The Aldactone® component of Aldactazide specifically blocks the sodium-retaining and potassium-excreting effects of aldosterone in the *distal* segment. This dual diuretic influence not only intensifies diuresis whenever aldosterone is a factor but also offsets the potassium loss induced by proximally acting diuretics. Therefore, potassium supplementation is not only unnecessary when Aldactazide is used as the sole diuretic agent but may rarely cause hyperkalemia.

Moreover, since resistance to diuretic therapy is frequently related to increased aldosterone activity, Aldactazide strikingly relieves edema and ascites in many patients who are partially or completely unresponsive to other diuretic regimens.

The usual *adult* dosage of Aldactazide is one tablet four times daily, although dosage may range from one to eight tablets daily, and in some patients intermittent therapy is adequate.

Aldactazide is supplied as compression-coated white tablets, each containing 75 mg. of Aldactone (brand of spironolactone) and 25 mg. of hydrochlorothiazide.

promotes excretion of sodium and water in
BOTH PROXIMAL AND DISTAL SEGMENTS
of the renal tubules to assure:

- PROMPT MAXIMAL DIURESIS
- CONTINUED OPTIMAL SAFETY

Descriptive literature and directions for use available in Physicians' New Product Brochure No. 32 from

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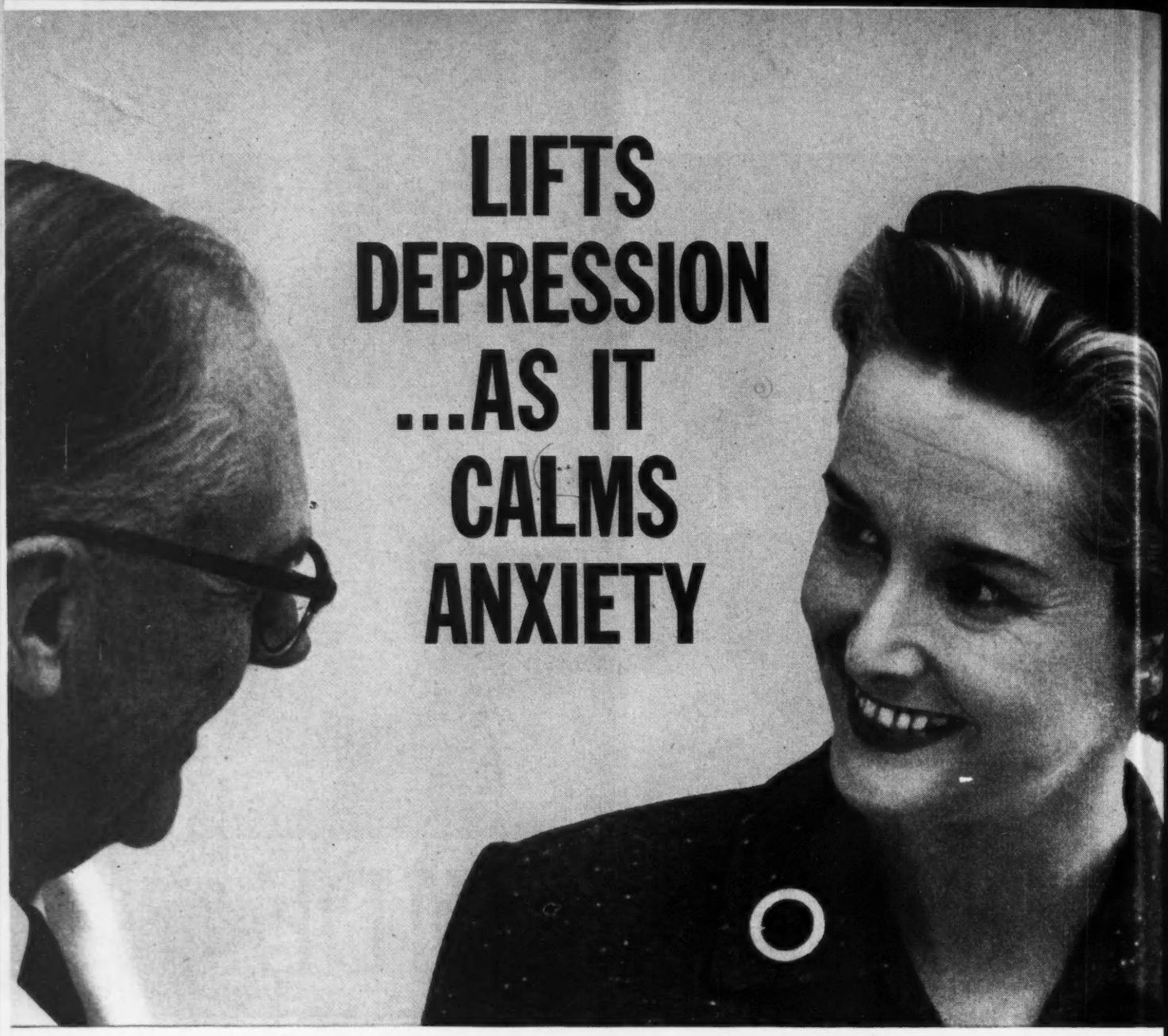
Research in the Service of Medicine

LIFTS DEPRESSION ...AS IT CALMS ANXIETY



"I feel like my old self again!" Thanks to your balanced Deprol therapy, her depression has lifted and her mood has brightened up – while her anxiety and tension have been calmed down. She sleeps better, eats better, and normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

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Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets.

Write for literature and samples.

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BOOK REVIEWS

EVALUATION OF DRUG THERAPY. Proceedings of the Symposium on Evaluation of Drug Therapy in Neurologic and Sensory Diseases held at the University of Wisconsin, May 1960. Edited by Francis M. Foster. 160 pp. The University of Wisconsin Press, Madison, Wis., 1961. $4.00.

This is a report of the proceedings of a symposium on evaluation of drug therapy in neurological and sensory diseases held at the University of Wisconsin in May 1960. It has six short, but generally very interesting, addresses on various aspects of drug evaluation given in general terms from different points of view. After 17 pages of prefatory remarks J. E. P. Toman begins with an excellent account of the pharmacological aspects of animal testing. W. H. Kessenich of the U.S. Food and Drug administration gives a clear and interesting account of the function of his department in the issuing of certification for marketing new drugs and the appraisal of evidence of safety and effectiveness. S. Jablon points out that a control group does not necessarily mean an untreated group: a controlled study is merely one in which there is a comparison. He mentions difficulties arising from different disease classifications, a point which is explored further by W. G. Cochran, who makes some interesting points with respect to the numbers needed for controlled studies: these can be surprisingly large. S. H. Ferebee issues a sound warning to all would-be investigators. Then follow reports from various panels set up to organize drug testing in epilepsy, vertigo, neuralgias and neuropathies, headache, glaucoma, multiple sclerosis, diseases of muscles and parkinsonianism.

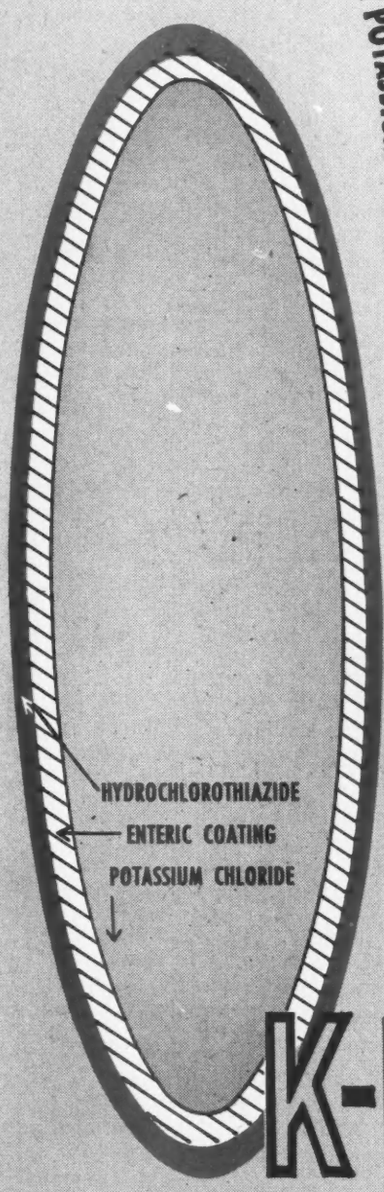
This book can be read in an evening and it should certainly be read by every clinical investigator.

ATTENUATED INFECTION: The Germ Theory in Contemporary Perspective. H. J. Simon, Assistant Professor in Medical Microbiology and Assistant Professor in Medicine, Stanford University School of Medicine. 349 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1960.

Infectious disease depends on more than virulence, resistance and the immune response. The details of the host-parasite interactions are important and involve genetics and numerous environmental factors. Terms such as masked, inapparent, occult, subclinical and latent will be familiar to all practitioners, whereas attenuated may be new.

Attenuated infection is defined as infection with a potentially pathogenic micro-organism which is not followed by overt disease. It represents a state of truce or peaceful coexistence between host and infecting agent and embraces the carrier state, microbial persistence and latent infection. Attenuated infection may become progressive infection and attenuation may follow overt infectious disease. As the author states in the introduction, the purpose of this work is to propose and illustrate with appropriate examples the concept that peaceful coexistence between organisms is the rule in nature rather than the exception. The relevant literature (there are nearly three hundred references) has been assembled and integrated for all kinds of parasites and for all forms of life. The examples range through plants, insects, animals, man and the bacteria-bacteriophage system. The dynamics

A NEW TECHNIQUE TO HELP PREVENT POTASSIUM DEPLETION WHILE TREATING EDEMA AND HYPERTENSION WITH



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K-Fluvin tablets permit administrati
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Contraindications:
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of and the factors known to influence attenuated infection are also presented. Two parts of the book, comprising over half of it, are devoted to a detailed discussion of attenuated infection in tissue culture and in man. Modern tissue culture techniques have provided the means to study some of the basic dynamics and mechanisms involved, and this section is full of interest. The other concept discussed is that the germ theory requires modification and amplification to include host and all the other factors shown to be important in the conversion of infection into progressive infection and infectious disease.

The book contains much valuable information relative to the subject and should be of interest to biologists in general, especially microbiologists and those who utilize tissue cultures. The practising physician will find the going fairly heavy in places. The author succeeds in showing that peaceful coexistence between host and infecting agent is a general phenomenon in nature.

THE STURGE-WEBER SYNDROME. G. L. Alexander and R. M. Norman. 95 pp. Illust. John Wright & Sons Limited, Bristol; The Macmillan Company of Canada Limited, Toronto, 1960. $5.50.

Many of the more chronic diseases or syndromes are due to the same causes: genetic, degenerative, traumatic or infectious, yet they may be designated by different names (or eponyms) based on the addition or subtraction of a symptom, or above all on some slight variation in geographical distribution. This applies particularly to disorders affecting the nervous system. Many a bold adventurer has added his eponym, because like Hudibras

> "He could distinguish and divide
> A hair, twixt south and south-west side."

Alexander and Norman have made such a venture in "The Sturge-Weber Syndrome", apparently with marked justification and certainly with considerable success.

In their monograph they display evidence of very wide research into seemingly all the recorded cases of this syndrome—real or conjectured. They also record seven of their personal cases, of which five were operated upon.

These as well as many other cases were subjected to intensive study, with comparison and differentiation. The lines of investigation were numerous and varied: anatomical, pathological, developmental, radiological, psychological, ophthalmological and dermatological. They even instituted chemical analysis of excised brain tissue and, above all, studies of the electroencephalographic recordings. They are particularly emphatic about the distribution of the "naevus flammeus", the well-known port wine stain.

In this disease, which shows up in infancy, the radiological evidence of calcification in the brain may be slow in appearing and the electroencephalographic indications inconclusive, yet early diagnosis is essential. They therefore advocate the very early use of electrocorticography (with the opening of the skull to apply this device) when other symptoms seem to justify it, for verification of the diagnosis—and then they recommend operation.

The implication of this fine piece of research can best be summed up by citing the authors' own conclusion:

"From the evidence presented in this monograph it would be reasonable to suppose that lobectomy, early in infancy, may offer a prospect of forestalling the onset of epilepsy and hereby perhaps avoiding the paresis and intellectual retardation, which is so very common in the Sturge-Weber disease. We submit that lobectomy in infancy is indicated if the Sturge-Weber lesion is present."

The reviewer can only add that this well-written and well-illustrated monograph is required reading for every neurosurgeon and of interest to any other practitioner who might come in contact with one of these relatively rare cases.

BLOOD GROUPS IN MAN. R. R. Race and Ruth Sanger, The Lister Institute, London, England. 377 pp. Illust. 3rd ed. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $8.50.

This is the standard reference work on blood groups for those in charge of blood banks, pathologists, geneticists and anthropologists. This review is not directed to specialists in the field, since they will already have the book. Readers, however, whose fields of interest fringe on the subjects of blood groups will be greatly surprised at the readability of this book, and grateful for the clarity of prose and style which arranges its subject matter from a bewildering picture to a clear and orderly pattern.

We are in the beginning of a new era of discovery about the inheritance of disease which, until recently, was virtually limited to those conditions which were inherited in a sex-linked pattern.

By the identification of family blood group patterns we now have the tools to investigate the way in which health, fertility and survival are affected by inheritance transmitted by the other 44 chromosomes.

The third edition of this work more than lives up to all the expectations of readers of the first and second editions.

THE ADRENAL CIRCULATION. R. G. Harrison and M. J. Hoey. 77 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $6.50.

Although a small number of non-specialist medical investigators will profit greatly from reading this slim monograph on the recent research undertaken by the authors on the adrenal glands, it is of great interest only to endocrinologists. Normally, the material presented could have been published as several modest papers in medical journals where, perhaps, it would have run a small risk of being overlooked. Its publication in book form, intended to avert this possibility, does not automatically guarantee a wider audience or even a greater dignity. In fact, one fears that this form of publishing may have the opposite result of effectively limiting the audience. Undoubtedly the authors were mercifully unaware of the Law of Nature concerning books enunciated by Sir William Osler in 1916: "The vast majority of books are dead, and not one in ten thousand has survived its author. Like the race of leaves the race of books is."

In conclusion, this book is highly recommended for purchase and possession only to those readers who find its honest title "The Adrenal Circulation" truly attractive.

CONGESTIVE FAILURE

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Keyes, J.W. and Berlacher, F.J.: J.A.M.A. 169:109, (Jan. 10) 1959.

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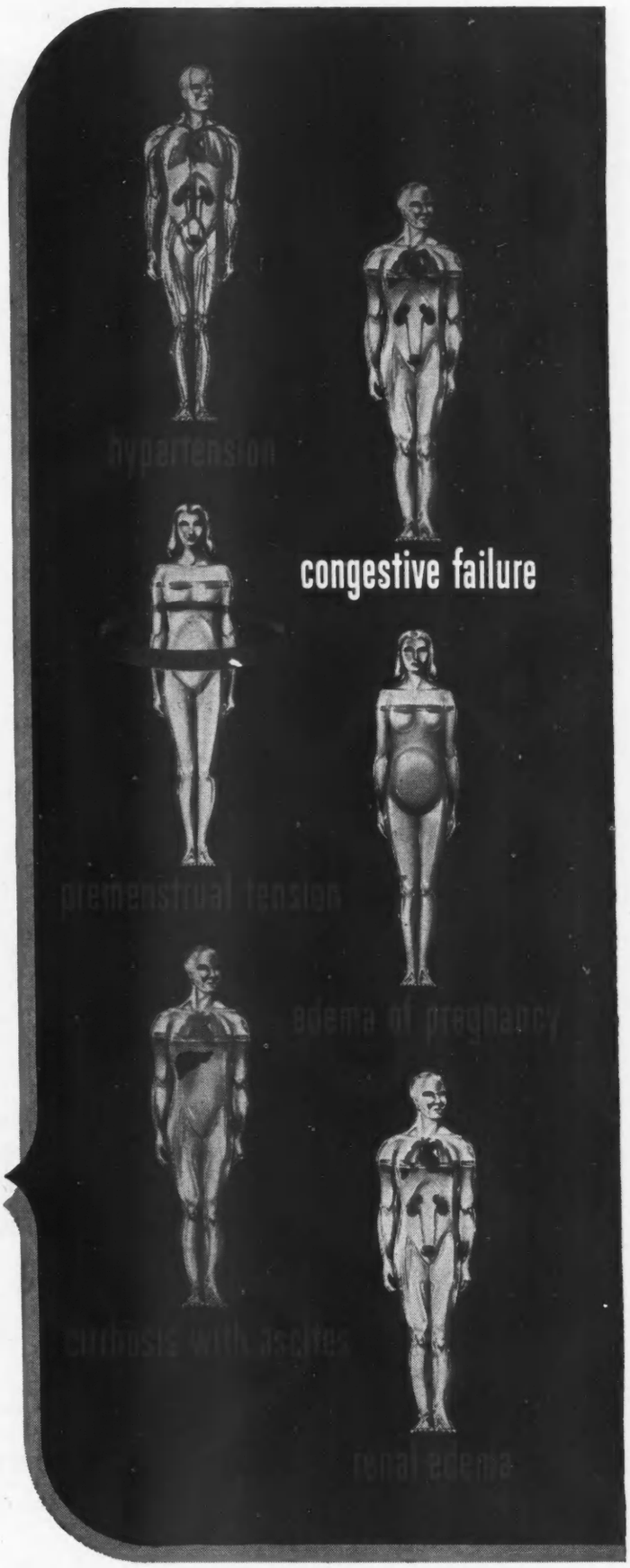

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MEDICAL NEWS *in Brief*

(Continued from page 1329)

SEVENTEENTH ANNUAL MEETING, SOCIETY OF OBSTETRICIANS AND GYNECOLOGISTS OF CANADA

The Seventeenth Annual Meeting of the Society of Obstetricians and Gynecologists of Canada—La Société des Obstetriciens et Gynécologues du Canada—will be held at The Chantecler, Ste-Adèle, Quebec, on June 16, 17 and 18, 1961. The scientific program is as follows:

Friday Morning, June 16

"Prolapse of the Cord", Dr. L. Rubin, Winnipeg; "Extraperitoneal Hemorrhage Following Manchester Repair", Dr. J. F. Moffat, Toronto; "The Treatment of Habitual Aborters by Psychotherapy", Dr. Carl Tupper, Halifax; "Primary Carcinoma of the Fallopian Tube—A Report of Eight Cases", Dr. Winifred M. Ross, Montreal; "The Organization of Maternity Services in Underdeveloped Countries", Dr. D. B. Stewart, Jamaica; "Genetics and Gynecologic Practice", Dr. John Parks, Washington, D.C.

Saturday Morning, June 17

"Observations on the Peritoneum as an Absorbing Surface", Dr. S. C. Robinson; "Ten-Year Survey of Pregnancy, Complicated by Diabetes, at Toronto General Hospital", Dr. J. W. Rogers; "Urethro-Vesico-Vaginal Fistulae", Dr. T. M. Roulston; "Abdominal Decompression During First Stage of Labour", Dr. R. A. McKeown, Montreal; "Operative Obstetrics", Dr. John Parks, Washington, D.C.; The President's Address, Dr. Elinor F. E. Black, Winnipeg.

Sunday Morning, June 18

"Ten Cases of Thecoma at the Women's College Hospital from 1954 to 1960", Dr. M. Yoneyama, Toronto; "An Evaluation of Fetal Electrocardiography", Dr. O. A. Schmidt, Winnipeg; "A Study of Amniotic Fluid in Iso-immunized Pregnancies", Dr. Maurice Mayer, Paris, France; "Estrogens and Capillary Strength", Dr. C. A. B. Clemetson, Saskatoon; "Postgraduate Training in Obstetrics and Gynecology", Dr. W. G. Green, Hamilton.

—

POSTGRADUATE COURSE IN OCCUPATIONAL MEDICINE

Occupational Medicine, a full-time course for physicians, will be given for eight weeks from September 18 to November 10, 1961, by the New York University Post-Graduate Medical School.

The course content covers the following areas: preventive medicine, including epidemiology and biostatistics, administrative medicine, occupational diseases, and industrial hygiene. It is aimed at meeting the need for specialized training in industrial medicine. Didactic instruction will be supplemented with field trips to industrial plants, governmental agencies concerned with industrial health, and union health centres. Opportunity will be given to attend medical, surgical and clinical-pathological conferences held in the New York University Medical Center.

The tuition fee is $375 and field expenses are $25.00.

For further information write: Office of the Associate Dean, NYU Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.

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TENTH INTERNATIONAL CONGRESS OF RADIOLOGY, MONTREAL, 1962

The Canadian Board of Management announces that members of medical radiological societies, radiobiologists, biophysicists, radiation physicists and scientists in cognate fields are cordially invited to become members or associates of the Tenth International Congress of Radiology and attend its sessions which will convene in Montreal, August 26 to September 1, 1962.

The scientific program and scientific exhibits will be arranged in four divisions: Diagnostic Radiology; Therapeutic Radiology; Radiobiology; Radiation Physics. Emphasis will be placed on recent advances in knowledge, especially since the last Congress, in the selection of invited and proffered scientific communications and scientific exhibits. Symposia on correlated subjects embracing two or more of the above fields and certain cognate sciences will be included.

Major topics selected for scientific papers and exhibits include: recent advances in image amplification, recording and transmission; roentgendiagnostic assessment of the effect of ionizing radiation; selective angiography in the investigation of organic disease; renal disease; clinical applications of cine-radiography; neurological and pediatric radiologic studies; radiation dose in diagnostic procedures; effects of ionizing radiation at cellular and sub-cellular levels; radiation protection including employment of medication and hypothermia; effect of internal emitters on body tissues; ionizing radiation in relation to carcinogenesis and leukemogenesis; total body irradiation, immunity mechanisms and marrow transplantation; genetic and population effects of ionizing radiation; external localization of pathological processes with radioactive isotopes; metabolized isotopes in therapeutic radiology; measurement *in vivo* of absorbed dose in tissues; advances in external beam therapy; advances in intracavitary and interstitial radiation therapy, and treatment planning.

The Preliminary Announcement containing information pertinent to membership enrolment, proffer of scientific papers and exhibits, hotel reservation, etc., is being sent to all qualified members of national medical radiological societies and other recommended scientists.

Further information from: Carleton B. Peirce, M.D., Secretary-General, Suite 204, 1555 Summerhill, Montreal 25, Quebec.

THIRD INTERNATIONAL CONGRESS OF PLASTIC SURGERY

The American Society of Plastic and Reconstructive Surgery and the American Association of Plastic Surgeons extend a cordial invitation to plastic surgeons throughout the world to participate in the Third International Congress of Plastic Surgery, convening at the Hotel Statler Hilton, Washington, D.C., October 13-18, 1963.

The Third International Congress will provide an opportunity for plastic surgeons to make new friends and renew old acquaintances among their professional colleagues in many lands and to exchange useful and stimulating scientific information.

The plastic surgeons of the United States are actively preparing a welcome for their colleagues. We invite you to join us in Washington and visit our homes, clinics and hospitals.

Address all communications to the Secretary General of the Congress: Leslie H. Backus, M.D., 217 Linwood Avenue, Buffalo 9, N.Y., U.S.A.

(Continued on page 34)

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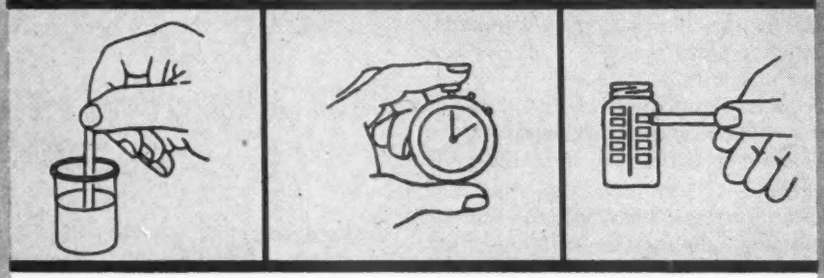

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MEDICAL NEWS *in brief*

(Continued from page 33)

ANNUAL SYMPOSIUM ON PULMONARY DISEASE, DENVER, COLORADO

The Fourteenth Annual Symposium on Pulmonary Disease will be held at Fitzsimons General Hospital, Denver, Colorado, September 25-29, 1961. This symposium is co-sponsored by the American Thoracic Society, the University of Colorado School of Medicine and Fitzsimons General Hospital. Registration fee is $5.00.

Information concerning enrolment may be obtained from the University of Colorado Medical School at Denver or from the Program Director, Colonel Charles S. Christianson, Chief, Pulmonary Disease Service, Fitzsimons General Hospital, Denver 30, Colorado.

THIRD INTER-AMERICAN CONFERENCE ON OCCUPATIONAL MEDICINE AND TOXICOLOGY

The Third Inter-American Conference on Occupational Medicine and Toxicology will be held at the Biscayne Terrace Hotel, Miami, Florida, from August 6 to 10, 1961. Scientific papers will be presented each morning from Monday, August 7, to Thursday, August 10, from 9 a.m. to 1 p.m. The scientific program will be devoted to papers on the following topics: Administrative Practices; Antibiotics and Other Drugs; Ionizing Microwave (Radar) Radiation; Medicine in the Tropics; Environmental Hygiene; Dermatology; Noise; Pesticides and Fungicides.

Official languages of the Conference will be English and Spanish.

The registration fee for delegates is $10.

For further information, correspondence should be directed to: William B. Deichmann, Ph.D., Professor of Pharmacology, University of Miami, School of Medicine, Coral Gables, Florida, U.S.A.

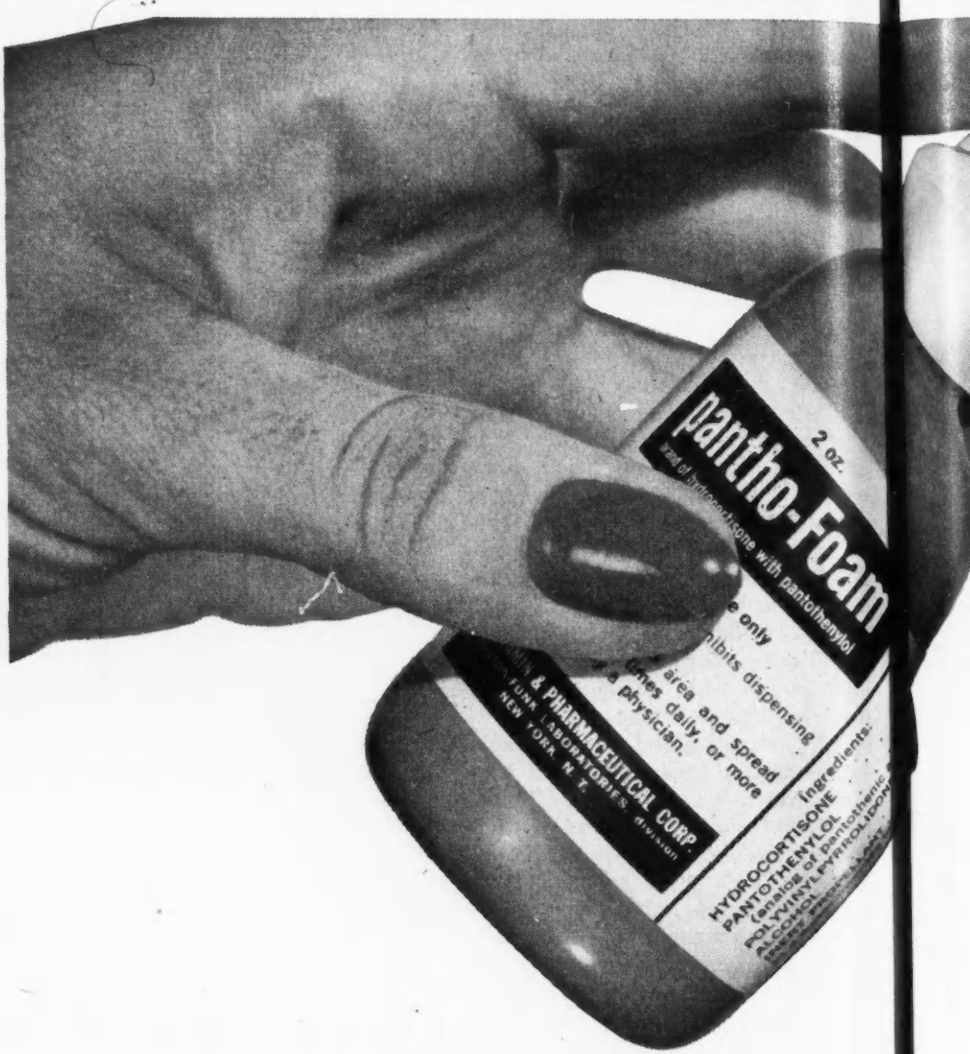
UNIVERSITY OF TORONTO GRADUATE APPOINTED CHAIRMAN OF DEPARTMENT OF PATHOLOGY AT UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

Dr. Emmanuel Farber, American Cancer Society research professor of pathology and biochemistry at Tulane University, New Orleans, will become professor and chairman of the Department of Pathology at the University of Pittsburgh School of Medicine. His appointment will become effective in July.

A native of Toronto, Dr. Farber received his medical degree at the University of Toronto Faculty of Medicine. He received his internship and residency training in pathology at the Hamilton General Hospital, Hamilton, Ontario.

Dr Farber served in the Royal Canadian Army Medical Corps from 1943 to 1946. He then attended graduate school at the University of California at Berkeley, where he received his Ph.D. degree in biochemistry. He was a fellow in cancer research, sponsored by the American Cancer Society, both at the University of California and at the Hektoen Institute for Medical Research, Cook County Hospital, Chicago.

Dr. Farber joined the faculty of Tulane University School of Medicine



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in 1950. He also has been visiting pathologist at Charity Hospital, New Orleans.

EMERGENCY MEDICAL IDENTIFICATION

The recent First National Conference on Emergency Medical Identification (U.S.) agreed on the need for a nation-wide educational campaign to acquaint the public with the value of carrying accurate health information with them at all times, and recorded the opinion that such information would be useful in rendering first aid treatment to unconscious persons suffering from a disease or sensitivity that might be aggravated by improper treatment.

Sponsored by the American Medical Association's Department of Health Education, the conference was attended by representatives of more than 60 national organizations.

Its purpose was to explore the feasibility of developing a voluntary nation-wide program whereby identifying and medical data would be readily available on the persons of individuals in emergency situations, to facilitate adequate care.

Delegates agreed that formation of a central organization to coordinate development of such a program was desirable and recommended that additional conferences be held.

Among the subjects discussed were the type of information persons should carry and how it should be carried. At present, there are in use a number of devices such as pocket cards, lockets, bracelets, watchbands and dog-tags.

Represented at the conference were medical, nursing and hospital associations, governmental and voluntary health and public health agencies, farm organizations, fire and police officers, the armed forces, civil defence agencies, youth service organizations, insurance companies and industrial groups.—*A.M.A. News*, May 1, 1961.

AMERICAN COLLEGE OF CHEST PHYSICIANS POSTGRADUATE COURSES

The Council on Postgraduate Medical Education of the American College of Chest Physicians will present the following postgraduate courses during 1961:

Cardiopulmonary Problems in Children: Brown Hotel, Denver, Colorado, July 24-28.

Industrial Chest Diseases: Warwick Hotel, Philadelphia, September 25-29.

Clinical Cardiopulmonary Physiology: Sheraton-Chicago Hotel, Chicago, October 23-27.

Recent Advances in the Diagnosis and Treatment of Heart and Lung Diseases: Park Sheraton Hotel, New York City, November 13-17.

Recent Advances in Diseases of the Chest: Statler-Hilton Hotel, Los Angeles, December 4-8.

Tuition for each course is $75 for members of the American College of Chest Physicians and $100 for nonmembers. The fee includes attendance at the round table luncheon discussions.

Further information may be obtained by writing the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Ill.

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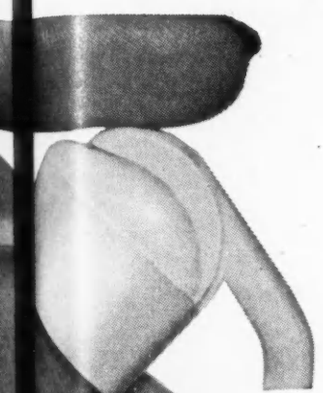

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MEDICAL NEWS *in brief*
(Continued from page 35)

GAINS IN CONTROL OF CANCER

Because of the heavy death toll from cancer, the encouraging gains made in the control of the disease tend to be overlooked, according to statisticians of Metropolitan Life Insurance Company.

Even though methods of treatment have been largely limited to surgery and radiation, much progress has been made in lengthening the life of cancer patients. The American Cancer Society estimates that if all patients received early and adequate treatment, one-half would survive at least five years after diagnosis of the disease.

Some indication of the effect of the detection of cancer at an early stage is provided by a study sponsored by the National Cancer Institute of the follow-up records of 117,000 patients from 99 hospitals in the United States.

For example, for male patients with cancer of the stomach, the five-year survival rate was 8%, while for those who received treatment at an early stage it was 30%. For cancer of the esophagus, the contrasting records were 2% and 24%; for cancer of the large intestine, 29% and 51%.

Among female patients, the importance of treatment at an early stage was just as marked. Against a 50% five-year survival record for breast cancer, 72% of patients receiving treatment at an early stage were still alive after five years. For ovarian cancer, the contrasting percentages were 24 and 60%.

These figures do not take into account deaths that would normally be expected from other causes. For that reason, survival rates so adjusted are materially higher than those shown.

—

ALLAN BLAIR MEMORIAL FELLOWSHIPS

The purpose of the Allan Blair Memorial Fellowships is to encourage junior members of the clinical staff of Canadian medical schools to continue clinical investigation in the field of cancer during the early years of their medical practice.

Applicants for these Fellowships must be graduates of an approved Faculty of Medicine and

(a) Shall have met the requirements of admission to the Royal College of Physicians and Surgeons of Canada.

(b) Shall have been appointed to membership, without salary, of the staff of one of the Faculties of Medicine in Canada.

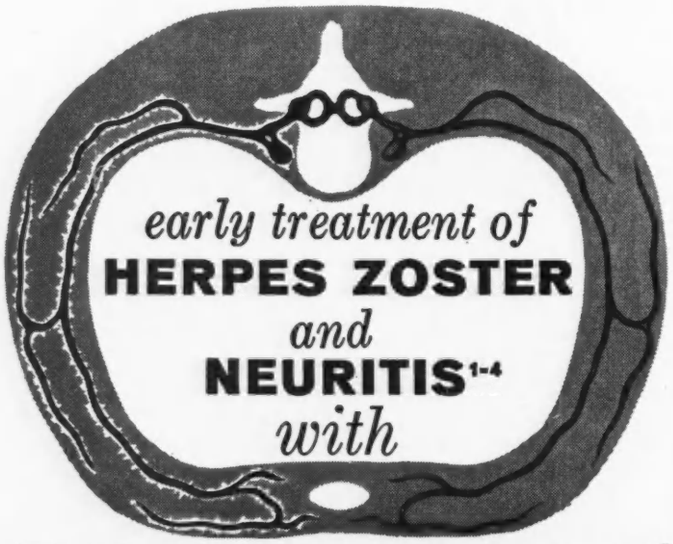
(c) Shall be responsible to the Head of the Department in which he holds an appointment and shall submit a plan of work, or a research project, approved by the Head of the Department, for the approval of the Advisory Committee. Such a plan should indicate the proportion of the candidate's time which will be devoted to the program.

One Fellowship will be awarded annually, tenable for three years. Each Fellow will be required to submit a progress report at the conclusion of each year of tenure.

The Fellowship will have a value of $4800.00 for the first year, $3600.00 for the second year, and $2400.00 for the third year.

Application forms may be obtained through the Dean of the respective Faculty of Medicine or from the Canadian Cancer Society, 790 Bay Street, Toronto 2, Ontario.

Applications should be submitted to the above address not later than October 1 in each year. The Award will be announced on or about November 15 and the Fellowship will become tenable on July 1 of the following year.



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References: 1. Baker, A. G.: Penn. Med. J. 63:697 (May) 1960. 2. Smith, R. T.: New York Med. (Aug. 20) 1952, pp. 16-19. 3. Smith, R. T.: Med. Clin. N. Amer. (Mar.) 1957. 4. Lehrer, H. W.; Lehrer, H. G., and Lehrer, D. R.: Northw. Med. (Nov.) 1955. 5. Sforzolini, G. S.: Arch. Ophthal. 62:381 (Sept.) 1959.

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